Journal of

CHRONIC DISEASES

VOL. 3 MARCH, 1956 NO. 3

Announcement

The Editors of the JOURNAL OF CHRONIC DISEASES take pleasure in listing the names and academic positions of the six members of the Editorial Board who were added last summer. They have been serving the interests of the JOURNAL for the past several months, although no previous notice has been made in its editorial columns.

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McGill University School of Medicine
Physician-in-Chief, Royal Victoria Hospital
Montreal, Quebec

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Harvard University
Boston, Massachusetts

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Northwestern University School of Medicine
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University of Pittsburgh School of Medicine
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Original Communications

RADIOACTIVE TRACER TESTS FOR THE RECOGNITION AND IDENTIFICATION OF VITAMIN B_{12} DEFICIENCY STATES

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(Received for publication Oct. 24, 1955.)

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INTRODUCTION

DIRECT methods for measuring the absorption of vitamin B_{12} have provided a stimulus to the study of pernicious anemia and allied disorders. The use of microbiologic and radioactive techniques have many advantages over the hematologic response of the patient with pernicious anemia in relapse as methods for the study of vitamin B_{12} absorption. The synthesis of vitamin B_{12} containing cobalt^{60} has made radioactive assays possible.[1]

In 1951, preliminary studies with Co^{60}-labeled vitamin B_{12} were carried out in which 5.0 μg of the vitamin were administered orally to patients with pernicious anemia and to normal individuals.[2] The feces were collected, dried and ashed, extracted with α-nitroso β-naphthol, and the cobalt electroplated on copper discs. The beta-radiation was then determined in a windowless flow counter. With this amount of vitamin B_{12}, more than 80 per cent of the administered radioactivity was excreted in the feces of both normal individuals and patients with pernicious anemia. The precision and convenience of scintillation counting have measurably improved the methods dependent on Co^{60}-labeled vitamin B_{12}. In 1952 Heinle and his associates[3] reported that when 0.5 μg of Co^{60} B_{12} was administered orally to patients with pernicious anemia, 72 to 96 per cent of the administered radioactivity was excreted in the feces. If these same amounts of labeled vitamin B_{12} were given with a source of intrinsic factor, the fecal excretion was significantly reduced. The importance of using a very small test dose was emphasized by the observations of Meyer[4,5] who showed that when 1.0 μg of Co^{60} B_{12} was used as the test dose, there was some overlap in the per cent excretion in the feces between normal individuals and patients with pernicious anemia. Using the radioactive technique, impaired absorption of vitamin B_{12} was demonstrated in patients after total gastrectomy and in patients

This work was carried out under Contract AT (30-1) 1208 between the Atomic Energy Commission and The Johns Hopkins University, and was supported in part by a grant from The National Vitamin Foundation.

with certain intestinal abnormalities.[6-11] In 1953 Schilling[12] was able to use the urinary excretion of radioactivity following an injection of 1,000 μg of vitamin B_{12} as a measure of absorption of a previously administered labeled oral dose. Glass and his co-workers[13] demonstrated that vitamin B_{12} absorption could also be measured by counting the increase in radioactivity over the liver after the oral administration of Co^{60} B_{12}.

The present report is concerned with the study of the absorption of vitamin B_{12} labeled with Co^{60} in normal individuals, in patients with a wide variety of clinical disorders not related to vitamin B_{12} deficiency, and in patients with diseases in which faulty vitamin B_{12} absorption is encountered.

MATERIALS AND METHODS

These studies were carried out in patients seen at The Johns Hopkins Hospital, the Baltimore City Hospitals,* and the Metabolism Unit of the Walter Reed Army Hospital.* The normal subjects were medical students and house officers.

In the initial studies normal individuals and patients with pernicious anemia were given 5.0 μg of Co^{60} vitamin B_{12}.† These subjects ingested the vitamin B_{12} in the morning one hour before breakfast. Urine was collected for 24 hours and feces for 6 days. Aliquots of urine were reduced in volume and ashed in a muffle furnace at 600° C. overnight. Three milligrams of inert cobalt in the form of cobaltous chloride ($CoCl_2.6H_2O$) were added to act as a carrier, and the residue was dissolved in concentrated hydrochloric acid on a steam bath. The resultant solution was reduced to a minimum volume, 100 ml. of 5 per cent hydrochloric acid were added, and the cobalt precipitated with α-nitroso β-naphthol. The precipitate was ashed in a muffle furnace at 600° C. overnight and dissolved in concentrated hydrochloric acid on a steam bath. The cobalt was electroplated on copper discs from a 5 per cent ammonium oxalate solution. The beta-radiation of these discs was determined in a windowless flow counter. The feces were weighed, homogenized with water, and aliquots of this homogenate were treated as described for urine and the radioactivity determined. After the preliminary experiments this method was abandoned because of its complexity and because complete recovery of radioactive cobalt was not uniformly achieved.

In most of our investigations, one of two methods employing scintillation counting was used. In both, the administered dose of Co^{60}-labeled vitamin B_{12} was contained in 120 ml. of water in a 150 ml. beaker. Each beaker was marked at three levels, and the administered radioactivity was determined at each level in a scintillation counter. The scintillation tube was mounted in a lead shield; a cupped plastic shield mounted over the tube protected it from accidental contamination and insured the reproducibility of the geometric relations. The radioactivity of urine or feces was determined by placing the specimen in the same beaker used for the administration of the Co^{60}-labeled vitamin B_{12} and

*We wish to thank the Baltimore City Hospitals and the Walter Reed Hospital for their aid in studying these patients.

†Generously supplied by Merck & Company through the courtesy of Dr. Charles Rosenblum. The nonradioactive vitamin B_{12} used in these studies was also supplied by Merck & Company.

counting the gamma-radiation under the same geometric conditions that applied to the oral dose. The results were expressed in per cent of radioactivity administered.

In one type of study, the Co^{60}-labeled vitamin B_{12} was administered orally in varying amounts one hour before breakfast. The subjects' total fecal excretions were then collected for 6 days in 2-day intervals. The feces were dried on a steam bath with an infrared lamp as an additional source of heat. Stools with high fat content were extracted with ethyl ether. The dried feces were ground in a meat-grinder, and the radioactivity was determined. In most instances, the specimen used for counting consisted of the entire residue of a 2-day collection. In the other type of study, a modification of the method described by Schilling[12] was employed. The fasting subjects were given 0.5 μg of radioactive vitamin B_{12} orally, and one hour later they received 1,000 μg of inert vitamin B_{12} intravenously. Urine was collected for 24 hours, and the total volume of the 24-hour excretion was reduced by evaporation to less than 100 ml. The radioactivity of the entire specimen was determined. In all studies the subjects were fasting, and care was taken that no vitamin preparations or other sources of vitamin B_{12} were ingested prior to the study.

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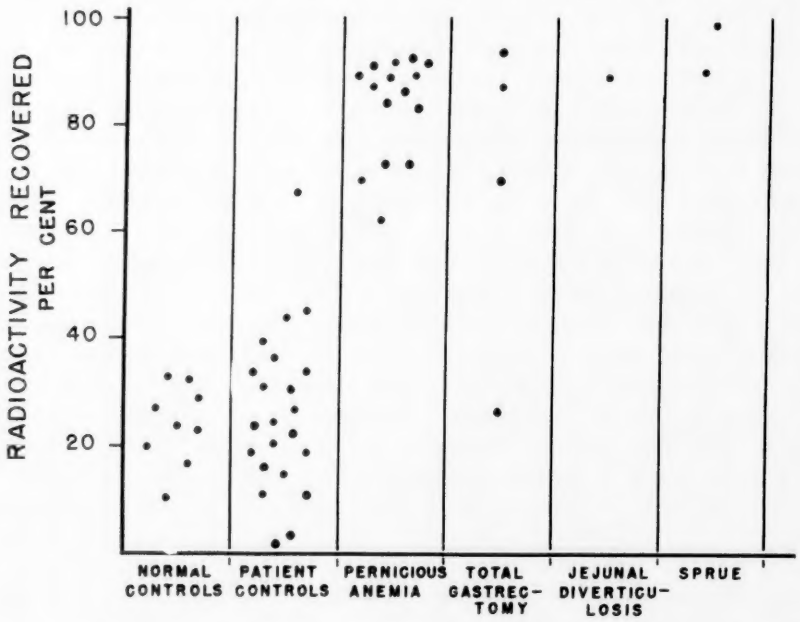

Fig. 1.—Radioactivity recovered in feces collected for 6 days following oral administration of 0.5 μg B_{12} labeled with Co^{60}.

RESULTS

1. *Absorption of Vitamin B_{12} by Normal Individuals and Patients With Diseases Unassociated With Vitamin B_{12} Deficiency.*—Twelve normal individuals were given 0.5 μg of labeled vitamin B_{12} orally. The radioactivity recovered

TABLE I. NORMAL SUBJECTS. RADIOACTIVITY RECOVERED IN FECES COLLECTED FOR 6 DAYS FOLLOWING ORAL ADMINISTRATION OF 0.5 μG OF Co^{60}-LABELED VITAMIN B_{12}

SUBJECT	AGE	COLOR	SEX	PER CENT RADIOACTIVITY RECOVERED			
				FIRST 48 HOURS	SECOND 48 HOURS	THIRD 48 HOURS	TOTAL
1. S.W.	31	W	M	No specimen	7.9	(72 hours) 1.8	9.7
2. I.H.	26	W	M	(72 hours) 12.0	6.6	1.3	19.9
3. C.H.	33	W	M	12.9	12.8	0.9	26.6
4. M.B.	23	W	M	5.1	27.0	(24 hours) 1.1	33.2
5. O.C.	23	W	M	1.8	22.1	No specimen	23.9
6. C.A.	30	W	M	14.5	1.1	0.9	16.5
7. P.S.	24	W	F	25.1	2.8	1.1	29.0
8. E.R.	25	W	F	10.8	4.4	7.7	22.9
9. M.R.	25	W	F	25.8	6.1	0.4	32.3
10. S.S.	26	W	M	35.0	4.6	0.4	40.0
11. J.K.	30	W	M	46.1	3.1	0.7	49.9
12. P.R.	26	W	M	35.8	6.1	0.7	42.6

in feces collected for 6 days thereafter ranged from 9.7 to 49 per cent of the administered dose (Table I, Fig. 1). Twenty-four studies were carried out in 22 patients with a variety of clinical disorders unrelated to vitamin B_{12} deficiency. These individuals received 0.5 μg of the radioactive vitamin and their feces were similarly assayed. The radioactivity recovered ranged from 3.3 to 45 per cent in 21 of these cases (Table II, Fig. 1). One patient (Table II, Case 3) excreted 67.2 per cent. The abnormal absorption in this individual was confirmed by an additional study in which 68.4 per cent of the radioactivity of an oral dose of 0.25 μg was recovered. This patient, a 21-year-old white man, was convalescing from acute hepatitis. There were no hematologic abnormalities or other evidences of vitamin B_{12} deficiency and only minimal chemical evidence of hepatic dysfunction at the time of the absorption tests. One of the stool specimens contained an adult Ascaris. Examination of this patient two years following the test revealed that he was in robust health and his blood was entirely normal.*

In two instances absorption tests were repeated on the same individual. The results show a wide variation (Table II, No. 21a and 21b and No. 22a and 22b). In the normal subjects and patient controls no correlation was noted between age and amount of vitamin B_{12} recovered in the feces (Fig. 2).

*We are indebted to Dr. M. M. Wintrobe, Salt Lake City, Utah, for follow-up studies on this patient.

TABLE II. PATIENT CONTROLS. RADIOACTIVITY RECOVERED IN FECES COLLECTED FOR 6 DAYS FOLLOWING ORAL ADMINISTRATION OF 0.5 μG OF Co^{60}-LABELED VITAMIN B_{12}

SUBJECT	AGE	COLOR	SEX	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED			
					FIRST 48 HOURS	SECOND 48 HOURS	THIRD 48 HOURS	TOTAL
1. J.R.	44	W	M	Asymptomatic achlorhydria	8.3	7.8	4.1	20.2
2. R.E.	56	W	F	Polycystic renal disease	0.2	1.4	1.7	3.3
3. R.D.	21	W	M	Hepatitis, convalescent; Ascariasis, asymptomatic	54.8	12.4	0	67.2
4. C.E.	75	W	M	Malnutrition	1.4	28.3	0.7	30.4
5. W.P.	60	W	M	Coronary artery disease	22.8	1.1	0.5	24.4
6. S.V.	65	W	M	Chronic lymphocytic leukemia	15.0	14.8	1.8	31.6
7. L.S.	54	W	M	Coronary artery disease	30.6	8.4	1.4	40.4
8. J.Y.	59	W	M	Coronary artery disease	24.0	14.5	1.3	39.8
9. H.P.	28	W	M	Rheumatoid arthritis	15.9	No specimen	2.8	18.7
10. M.I.	27	W	M	Chronic hepatitis	No specimen	11.6	No specimen	11.6
11. A.M.	39	W	M	Gout	22.0	7.8	6.3	36.1
12. E.S.	20	W	M	Hepatitis	1.1	11.6	1.5	14.2
13. B.R.	1	C	M	Congenital heart disease	22.1	4.2	0.4	26.7
14. F.R.	½	C	F	Dermatitis	4.8	2.4	0.2	7.4
15. M.G.	14	C	M	Rheumatic heart disease	8.2	0.3	No specimen	8.5
16. D.D.	24	C	F	Acute rheumatic fever	0.1	1.2	(96 hours) 4.0	5.3
17. R.C.	53	W	F	Rheumatoid arthritis	14.6	7.5	(72 hours) 0.2	22.3
18. N.B.	75	C	F	Polyneuritis	9.2	0.4	(96 hours) 0.5	10.1
19. Be.M.	54	C	M	Anemia due to infection	22.6	3.0	(72 hours) 0.2	25.8

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TABLE II.—Cont'd

SUBJECT	AGE	COLOR	SEX	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED			
					FIRST 48 HOURS	SECOND 48 HOURS	THIRD 48 HOURS	TOTAL
20. S.C.	48	C	M	Myocardial infarct	9.6	6.2	(72 hours) 0.7	16.5
21a. J.C.*	55	C	M	Cerebral arterio-sclerosis	27.3	14.0	3.7	45.0
21b. J.C.*	55	C	M	Cerebral arterio-sclerosis	24.1	6.3	0.5	30.9
22a. H.G.†	66	C	M	Arteriosclerosis	2.1	10.6	5.5	18.2
22b. H.G.†	66	C	M	Arteriosclerosis	4.9	19.7	9.5	34.1

*†These represent successive studies on the same subjects under the same conditions.

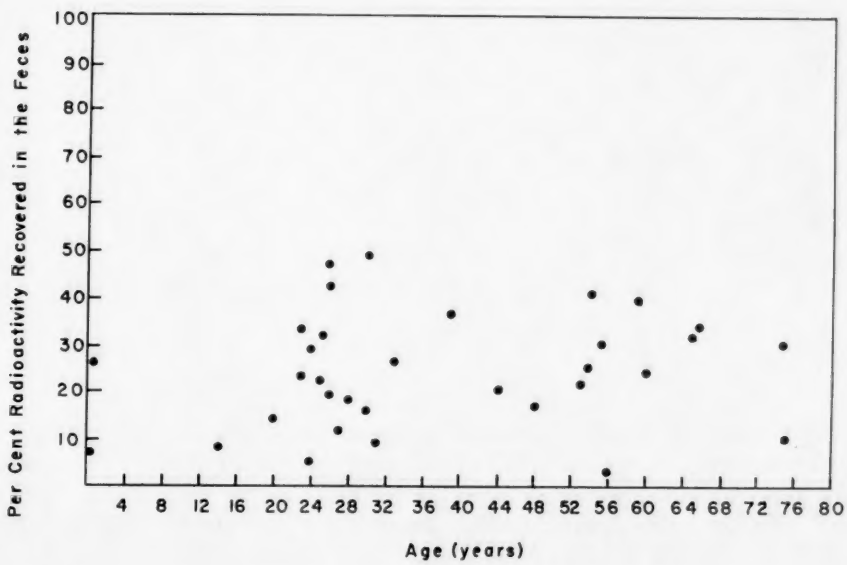

Fig. 2.—Relationship between age and per cent of radioactivity recovered in the feces following the oral administration of 0.5 μg of Co^{60}-labeled vitamin B_{12} in 32 subjects.

The relationship between the amount of vitamin B_{12} administered and the fraction recovered in the feces was studied in 16 individuals, of whom 6 were normal subjects (Table III). The per cent radioactivity recovered in the feces was not significantly altered by reducing the dose from 0.5 μg to as low as 0.1 μg. On the other hand, when the amount of labeled vitamin B_{12} was increased to 1.0 μg or more, a much larger fraction of the administered radioactivity was recovered in the feces.

TABLE III. RADIOACTIVITY RECOVERED IN THE FECES COLLECTED FOR 6 DAYS FOLLOWING ORAL ADMINISTRATION OF VARYING AMOUNTS OF Co^{60}-LABELED VITAMIN B_{12}

SUBJECT	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED IN FECES				
		0.1 μG B_{12}	0.25 μG B_{12}	0.5 μG B_{12}	1.0 μG B_{12}	5.5 μG B_{12}
1. S.S.	None	47.6		40.0		
2. B.R.	Congenital heart disease	20.3		26.7		
3. F.R.	Dermatitis	7.9		7.4		
4. M.G.	Rheumatic heart disease	15.8		8.5		
5. R.D.	Hepatitis		68.4	67.2		
6. R.M.	Jejunal diverticulosis		89.9	88.5		
7. T.E.	Sprue		103.4	89.9		
8. C.A.	None		19.4	16.5		
9. E.S.	Hepatitis		11.8	14.2		
10. A.M.	Gout		14.3	36.1		
11. M.I.	Hepatitis		8.1	11.6		
12. H.P.	Arthritis		38.1	18.7		
13. P.S.	None			29.0	60.4	
14. E.R.	None			22.9	43.9	
15. O.C.	None			23.9		78.1
16. M.B.	None			33.2		73.3

The modified Schilling test was performed on 6 normal individuals. In several the test was repeated. The results are shown in Table IV. The radioactivity excreted in the urine ranged from 10 to 37.5 per cent of that administered. Fifteen patients without clinical evidence of vitamin B_{12} deficiency were studied by this procedure and the urinary excretion varied from 7.3 to 21.1 per cent. This group included patients with histamine-fast achlorhydria, subtotal gastrectomy and cystic fibrosis of the pancreas (Table IV, Fig. 3).

2. *Absorption of Vitamin B_{12} by Patients With Clinical Evidences of Vitamin B_{12} Deficiency.*—

Dietary vitamin B_{12} deficiency: One patient was encountered who may have had vitamin B_{12} deficiency on a dietary basis.

D.T., JHH #482574, a 76-year-old white man, was admitted because of severe anemia, mental confusion, and neurologic abnormalities suggestive of subacute combined degeneration. He had subsisted for many years on a diet consisting largely of alcohol and potatoes. Initial blood studies

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showed the hematocrit value to be 10.9 per cent, red blood cell count 879,000 per cubic millimeter, hemoglobin 3.7 Gm. per 100 ml., M.C.V. 125, M.C.H. 42, M.C.H.C. 34, white blood cell count 1,200 per cubic millimeter, and platelet count 13,000 per cubic millimeter. The marrow pattern was typically megaloblastic. No free acid was present in the gastric secretion after the injection of histamine. Following the administration of parenteral vitamin B_{12} and blood transfusions, his blood picture returned to normal and he has subsequently maintained a complete hematologic remission. His cerebration returned to normal and his neurologic abnormalities improved.

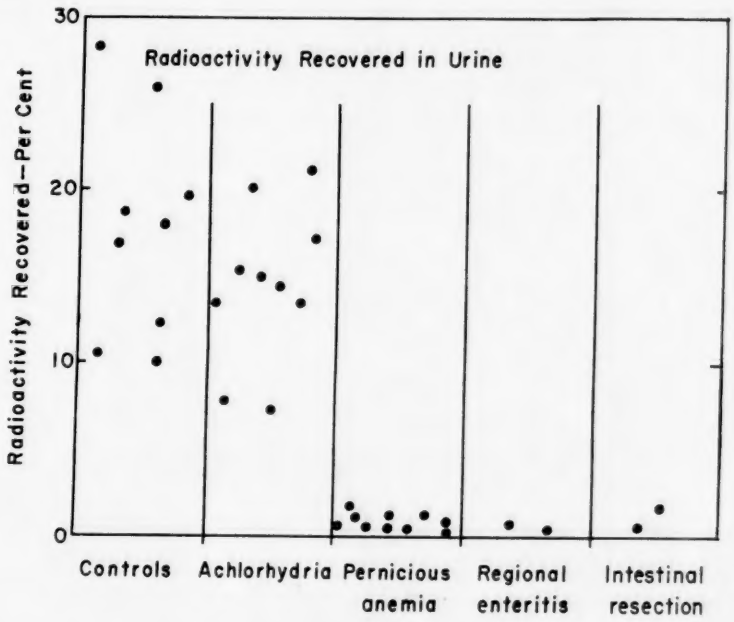

Fig. 3.—Urine was collected for 24 hours after the oral administration of 0.5 μg Co^{60}-labeled vitamin B_{12} followed in one hour by the intravenous administration of 1,000 μg of inert vitamin B_{12}. The radioactivity excreted in the urine was determined and expressed as per cent of the administered radioactivity.

The character of the neurologic manifestations suggest that this patient's anemia may have been due to B_{12} deficiency rather than to deficiency of folic acid. This patient was demonstrated to have normal absorption of vitamin B_{12} on two separate fecal excretion tests (Table V). In addition, a Schilling test performed subsequently (Table IV, Case 13) gave a normal result.

Deficiency of intrinsic factor: Vitamin B_{12} deficiency states due to lack of intrinsic factor are encountered in classical pernicious anemia and following total gastrectomy. Fifteen patients with pernicious anemia received 0.5 μg of labeled vitamin B_{12}. The radioactivity recovered in the feces ranged from 62.1 to 91.7 per cent of the amount administered (Table VI, Fig. 1). In one patient, only 49.4 per cent of the radioactivity was recovered. In this study 25.6 per cent was excreted on the sixth day, suggesting that a larger fraction would have been recovered if the study had been prolonged. Therefore, the test

TABLE IV. RADIOACTIVITY RECOVERED IN THE URINE COLLECTED FOR 24 HOURS AFTER THE ORAL ADMINISTRATION OF 0.5 μG OF Co^{60}-LABELED VITAMIN B_{12} FOLLOWED BY THE INTRAVENOUS INJECTION OF 1,000 μG OF INERT VITAMIN B_{12}

SUBJECT	AGE	COLOR	SEX	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED
1. M.P.	34	W	M	None	26.9
2. N.D.	30	W	F	None	37.5
3. E.H.	45	C	M	None	17.3
4. E.G.	22	W	M	None	28.9
5. C.G.	25	C	F	None	10.0
6. S.B.	65	C	M	None	19.9
7. C.O.	85	W	M	Arteriosclerosis	10.5
8. J.S.	49	W	F	Achlorhydria*	7.7
9. P.B.	24	W	F	Ulcerative colitis	18.7
10. L.B.	42	C	F	Achlorhydria*	7.3
11. L.E.	31	W	F	Achlorhydria*	20.6
12. G.B.	52	W	M	Polyneuritis, achlorhydria*	13.5
13. D.T.	76	W	M	Nutritional megaloblastic anemia	13.6
14. E.P.	55	W	F	Subtotal gastrectomy	12.2
15. C.W.	49	W	F	Achlorhydria,* diarrhea	18.6
16. R.M.	48	W	F	Achlorhydria*	15.2
17. S.W.	6	W	F	Cystic disease of the pancreas	9.3
18. H.C.	66	W	M	Refractory anemia	18.7
19. H.J.	40	W	F	Achlorhydria*	14.2
20. M.A.	65	W	F	Refractory anemia	21.1
21. J.O.	67	W	F	Achlorhydria,* splenomegaly	14.4
22. J.M.	66	C	F	Pernicious anemia	1.3
23. F.G.	52	W	M	Pernicious anemia	0.4
24. I.H.	67	W	F	Pernicious anemia	1.3
25. M.R.	72	W	F	Pernicious anemia	0.7
26. C.M.	64	C	M	Pernicious anemia	1.8
27. A.B.	53	C	F	Pernicious anemia	0.6
28. A.O.	13	W	F	Pernicious anemia	0.2
29. J.T.	84	W	M	Pernicious anemia	0.2
30. J.W.	61	W	M	Pernicious anemia	0.8

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TABLE IV. CONT'D.

SUBJECT	AGE	COLOR	SEX	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED
31. N.V.	69	C	M	Total gastrectomy	0.2
32. R.B.	28	W	F	Ileitis, intestinal blind loop	0.7
33. J.B.	30	W	M	Ileitis, malabsorption	0.4
34. J.M.	34	W	F	Small bowel resection for mesenteric thrombosis	0.5
35. F.H.	24	W	F	Small bowel resection for volvulus	1.4

*After injection of histamine.

TABLE V. NUTRITIONAL MEGALOBLASTIC ANEMIA. RADIOACTIVITY RECOVERED IN FECES COLLECTED FOR 6 DAYS FOLLOWING ORAL ADMINISTRATION OF 0.5 μG OF Co^{60}-LABELED VITAMIN B_{12}

SUBJECT	AGE	COLOR	SEX	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED			
					FIRST 48 HOURS	SECOND 48 HOURS	THIRD 48 HOURS	TOTAL
1. D.T.	76	W	M	Nutritional megaloblastic anemia	2.9	25.3	6.4	34.6
					10.8	1.6	0.9	13.3

was repeated, and on this occasion 91.2 per cent of the administered radioactivity was excreted in the feces. One patient with pernicious anemia received 2.0 Gm. of oxytetracycline (Terramycin) daily for 3 weeks. During the third week a radioactive vitamin B_{12} absorption test was performed and 86.9 per cent was excreted in the feces.

Nine additional patients with pernicious anemia were studied by the modified Schilling procedure. In every instance the urinary excretion of radioactivity was far below that encountered in the normal group, the highest value being 1.8 per cent (Table IV). In 3 of these patients the test was repeated, combining 0.5 μg of labeled vitamin B_{12} with 50 mg. of an intrinsic factor concentrate.* In all three the urinary excretion was increased to within the normal range (Table VII).

Four patients who had been subjected to total gastrectomy were studied by the fecel excretion technique (Table VI, Fig. 1). Three of these excreted more than 69 per cent of the radioactivity of a 0.5 μg dose. In the fourth case only

*The intrinsic factor concentrate used in these studies was generously supplied by Dr. K. W. Thompson of Organon, Inc., Orange, N. J. One U. S. P. unit corresponds to 35.5 mg. of this material, which is practically free of vitamin B_{12}.

TABLE VI. PATIENTS WITH DISEASES ASSOCIATED WITH IMPAIRED VITAMIN B_{12} ABSORPTION. RADIOACTIVITY RECOVERED IN FECES COLLECTED FOR 6 DAYS FOLLOWING ORAL ADMINISTRATION OF 0.5 μG OF Co^{60}-LABELED VITAMIN B_{12}

SUBJECT	AGE	COLOR	SEX	CLINICAL DISORDER	PER CENT RADIOACTIVITY RECOVERED			
					FIRST 48 HOURS	SECOND 48 HOURS	THIRD 48 HOURS	TOTAL
1. M.V.	67	W	M	Pernicious anemia	69.9	15.4	2.0	87.3
2. C.W.	41	C	F	Pernicious anemia	82.7	0.6	4.6	87.9
3. H.M.	62	W	F	Pernicious anemia	59.6	31.0	0.6	91.2
4. E.H.	38	C	F	Pernicious anemia	77.7	12.2	0.2	90.1
5. L.A.	50	C	M	Pernicious anemia	58.6	30.9	1.4	90.9
6. L.T.	62	W	F	Pernicious anemia	78.0	7.1	(72 hours) 0.7	85.8
7. L.P.	54	C	F	Pernicious anemia	0.1	82.0	(96 hours) 0.3	82.4
8. H.C.	79	W	M	Pernicious anemia	(96 hours) 66.3	(72 hours) 6.4	0.8	73.5
9. K.N.	66	W	F	Pernicious anemia	83.5	4.2	0.6	88.3
10. Ma.B.	51	W	F	Pernicious anemia	(96 hours) 72.5	1.0	(24 hours) 0.2	73.7
11. V.M.	53	W	F	Pernicious anemia	39.8	43.3	3.8	86.9
12. N.K.	51	C	F	Pernicious anemia	59.7	1.5	0.9	62.1
13. I.M.	74	W	F	Pernicious anemia	5.8	57.8	25.8	89.4
14. T.L.	52	W	M	Pernicious anemia	No specimen	55.4	(72 hours) 36.3	91.7
15. M.L.	56	W	F	Pernicious anemia	15.3	32.6	(96 hours) 22.0	69.9
16. S.T.	59	W	F	Sprue	94.0	4.6	No specimen	98.6
17. S.T.*	59	W	F	Sprue	80.2	3.8	0.5	84.5
18. T.E.	28	W	M	Sprue	85.3	3.7	0.9	89.9
19. B.C.	79	W	M	Total gastrectomy	22.6	2.3	1.6	26.5
20. W.C.	57	W	M	Total gastrectomy	31.9	59.0	1.6	92.5
21. G.S.	71	W	M	Total gastrectomy	68.8	0.3	0.4	69.5
22. H.D.	58	C	M	Total gastrectomy	73.4	12.4	(24 hours) 1.6	87.4
23. R.M.	59	C	M	Jejunal diverticulosis	62.8	23.4	(96 hours) 2.3	88.5

*This represents a repeat study of patient S.T. after cortisone therapy was instituted.

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TABLE VII. VITAMIN B_{12} ABSORPTION STUDIES EMPLOYING THE FECAL EXCRETION AND URINARY EXCRETION PROCEDURES UNDER VARYING CONDITIONS IN NORMAL INDIVIDUALS AND IN PATIENTS WITH CLINICAL DISORDERS

SUBJECT	CLINICAL DISORDER	FECAL EXCRETION STUDIES (NORMAL < 50% EXCRETION)		
		0.5 μG B_{12}	0.5 μG B_{12} + INTRINSIC FACTOR	0.5 μG B_{12} AFTER ANTIBIOTIC
1. R.M.	Jejunal diverticulosis	(%) 88.5		(%) 46.7
2. V.M.	Pernicious anemia			85.9
		"SCHILLING TESTS" (NORMAL > 7% URINARY EXCRETION)		
		0.5 μG B_{12}	0.5 μG B_{12} + INTRINSIC FACTOR	0.5 μG B_{12} AFTER ANTIBIOTIC
3. E.H.	None	(%) 17.3	(%) 17.0	(%)
4. J.O.	Achlorhydria, splenomegaly	14.4	25.1	
5. A.O.	Pernicious anemia	0.2	21.3	
6. F.G.	Pernicious anemia	0.4	13.7	
7. J.W.	Pernicious anemia	0.8	21.3	
8. F.H.	Intestinal resection	1.4	2.8	
9. J.M.	Intestinal resection	0.5	0.6	0.9
10. J.B.	Regional ileitis	0.4	0.4	0.6

26.5 per cent was recovered. It is noteworthy in this case that the test was performed three weeks after gastrectomy, whereas in the other patients the gastrectomy was remote.

An additional patient was studied by the Schilling technique and his urinary excretion was in the same low range found in pernicious anemia (Table IV, Case 31).

Disorders of absorption in the small intestine: Certain disorders of the small intestine are characterized by multiple absorption defects. Vitamin B_{12} deficiency on this basis has been encountered in sprue and in regional enteritis. Six studies employing the fecal excretion technique were carried out in 3 patients with sprue. In 2 cases an oral dose of 0.5 μg of the labeled vitamin was employed and the fecal excretion ranged between 84.5 and 98.6 per cent. Both of these patients had macrocytic anemia. The third patient was studied after the ingestion of 0.25 μg. In two successive studies the radioactivity recovered was 22.6 per cent and 33.7 per cent. It is noteworthy that this patient never had anemia.

Schilling tests were performed on two patients with regional enteritis who had clinical manifestations suggestive of vitamin B_{12} deficiency. In both absorp-

tion of vitamin B_{12} was impaired as evidenced by the low urinary excretion of radioactivity (Table IV).

J.B., JHH #438281, a white male physician, was 26 years old when first admitted to the hospital for evaluation of his chronic gastrointestinal disease. He was known to have had regional enteritis and anemia, and had previously had an ileocolostomy. Physical examination showed pallor, edema of the legs, impaired perception of vibration in the feet, and impaired 2 point discrimination in the distal portions of the arms and legs. The hematocrit value was 32.5 per cent, red blood cell count 2.8 million per cubic millimeter, hemoglobin 11.5 Gm. per 100 ml., and the white blood cell count 6,800 per cubic millimeter. The bone marrow was megaloblastic. The gastric secretion contained free acid. A prolonged prothrombin time returned to normal after the injection of vitamin K. The serum iron was extremely low (12.8 μg per 100 ml.). On therapy with folic acid, vitamin K, vitamin B_{12}, iron, and a high calorie-low residue diet, he became asymptomatic and the anemia disappeared. He has been maintained in good health on this regimen.

When the Schilling test was performed on this patient, only 0.4 per cent of the radioactivity was recovered in the urine. The test was repeated with the addition of 50 mg. intrinsic factor concentrate, and again only 0.4 per cent was excreted in the urine. The patient was then given 1.0 Gm. of chlortetracycline (Aureomycin) daily for two weeks, at the end of which time the Schilling test was repeated. On this occasion the urinary excretion was 0.6 per cent (Table VII, Case 10).

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R.B., JHH #554869, a white woman, was 23 years old in 1949 when she was discovered to have regional enteritis. A short-circuiting operation was performed and a long blind loop of involved small bowel was not resected. Following this her abdominal symptoms improved but she continued to have intermittent indigestion. She was first seen at this hospital in 1954 at which time she complained of intermittent diarrhea and soreness of the mouth and tongue. Physical examination was unremarkable but the laboratory studies revealed a mild normocytic anemia with an hematocrit value of 36.9 per cent. X-rays of the intestinal tract showed no detectible abnormality of the small intestine and the blind loop was not visualized. Following the parenteral administration of vitamin B_{12} the soreness of the tongue promptly subsided. The hematocrit value has remained at about 39 per cent.

Defective absorption of vitamin B_{12} was demonstrated in 2 patients following resection of a large segment of the small intestine (Table IV).

J.M., JHH #327900, a 32-year-old white woman with rheumatic heart disease, was admitted to the hospital in 1955 complaining of a sudden onset of abdominal pain and bloody diarrhea. Her past admissions had established the diagnosis of rheumatic heart disease with mitral stenosis and insufficiency and auricular fibrillation. On physical examination there was diffuse abdominal tenderness. On March 15, 1955, an operation was performed and the distal half of the jejunum, the entire ileum, and the cecum and ascending colon were resected because of gangrenous changes secondary to mesenteric embolus. Following operation, the patient had bulky, greasy stools and has continued to have intermittent congestive heart failure.

Vitamin B_{12} absorption studies were performed on this patient two months after surgery. On the initial Schilling test 0.5 per cent of the administered radioactivity was excreted in the urine. The test was repeated with the addition of 50 mg. of intrinsic factor concentrate, and only 0.6 per cent was recovered in the urine. The patient was then given 1.0 Gm. of chlortetracycline (Aureo-

mycin) daily for 10 days, at the end of which time the Schilling test was repeated and 0.9 per cent was recovered in the urine (Table VII, Case 9).

F.H., JHH #702649, a 25-year-old white woman, was admitted to the hospital complaining of abdominal pain and vomiting of five days' duration. On physical examination the abdomen was distended and tender to palpation. On April 23, 1955, an operation was performed and a volvulus of the small bowel was discovered. The small intestine from the proximal jejunum to the terminal ileum was resected. Only 18 inches of small intestine were left in place. After operation the patient excreted bulky stools for several weeks but these gradually diminished and at the present time she has 2 or 3 formed stools daily.

Two months after operation a Schilling test was performed and the patient excreted 1.4 per cent of the administered radioactivity in the urine. The study was repeated with 50 mg. of intrinsic factor concentrate and 2.8 per cent was recovered in the urine (Table VII, Case 8).

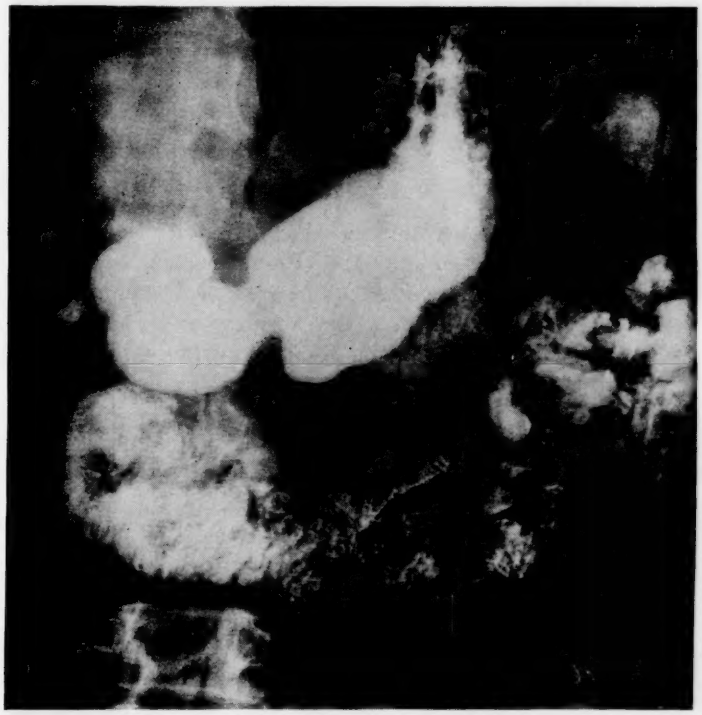

Fig. 4.—Photograph of a gastrointestinal x-ray film of patient R. M. showing jejunal diverticula.

Competition for available vitamin B_{12} by intestinal organisms or parasites: Vitamin B_{12} deficiency has occasionally been encountered in individuals with strictures and blind loop lesions of the small intestine and is well known to occur in some patients infested with the fish tapeworm, *Diphyllobothrium latum*. One patient with jejunal diverticulosis associated with a pernicious anemia-like syndrome was studied.

R.M., JHH #537240, a 59-year-old Negro man, had been referred to the Psychiatry Clinic in 1950 because of nervousness and abdominal distress. A history of numbness of the fingers and toes of three months' duration was elicited. Neurologic examination showed typical evidencee of subacute combined degeneration. Results of laboratory studies included an hematocrit valus of 25.9 per cent, red blood cell count 2.32 million per cubic millimeter, hemoglobin 8.4 Gm. per 100 ml., M.C.V. 112, M.C.H. 36, M.C.H.C. 32, and white blood cell count 4,250 per cubic millimeter. The bone marrow contained many typical megaloblasts. Abundant free acid was present in the gastric secretion after the injection of histamine. Gastrointestinal x-rays revealed numerous jejunal diverticula (Fig. 4). The patient was given a single oral dose of 5,000 μg vitamin B_{12} without gastric juice or any other source of intrinsic factor. On the fifth day reticulocytes rose to 30.2 per cent and there was prompt clinical improvement and subsequent return of the blood to normal. The patient has been maintained in complete remission for five years by the intramuscular injection of 45 μg of vitamin B_{12} once each six weeks. His neurologic examination is now entirely normal.

The patient was given 0.5 μg of labeled vitamin B_{12} and 88.5 per cent of the radioactivity appeared in the feces. Subsequently this test was repeated, using an oral dose of 0.25 μg, and 89.9 per cent was recovered. The patient was then given 1.0 Gm. of chlortetracycline (Aureomycin) daily for two weeks. On the fourteenth day the vitamin B_{12} tracer study was repeated, using 0.5 μg, and on this occasion only 46.7 per cent of the administered radioactivity was excreted in the feces (Table VII, Case 1).

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DISCUSSION

There are a number of mechanisms which might cause vitamin B_{12} deficiency. Inadequate dietary intake of the vitamin over a long period of time theoretically could lead to the appearance of the clinical manifestations of pernicious anemia. However, in areas of the world where other nutritional deficiencies are common, pernicious anemia is rare. Furthermore, the discontinuance of therapy in patients with pernicious anemia may be followed by a prolonged period during which evidences of vitamin B_{12} deficiency do not reappear. These observations are probably explained by the minute daily requirement for vitamin B_{12},[14] storage of the vitamin in the liver and other organs, and possibly by the synthesis of vitamin B_{12} by the bacterial inhabitants of the gastrointestinal tract. Few cases have been reported in which clinical vitamin B_{12} deficiency was attributed to an inadequate diet.[15] In such cases it is difficult to be sure that the disorder is not due to folic acid deficiency since a therapeutic response to vitamin B_{12} does not necessarily mean vitamin B_{12} deficiency. It is well known that clinical manifestations due to deficiency of either of these vitamins may respond to the administration of the other. We encountered only one patient in whom inadequate diet may have been the mechanism responsible for the development of vitamin B_{12} deficiency. A definitive diagnostic procedure, which was not performed in our case, would have been the demonstration of a low serum B_{12} level in conjunction with the normal B_{12} absorption.

Increased utilization as a cause for vitamin B_{12} deficiency is virtually unknown. One remarkable patient seen in our clinic had a megaloblastic anemia associated with myelofibrosis and myeloid metaplasia of the liver and spleen. The anemia responded to the parenteral administration of vitamin B_{12}, but doses much larger than those used for pernicious anemia were necessary.[16]

Deficiency in binding of vitamin B_{12} in the serum was considered by Horrigan and Heinle[17] to be the cause of a refractory macrocytic anemia in a patient studied by them. This case has not been reported in detail and no other similar cases have been recognized.

The majority of clinical vitamin B_{12} deficiency states are due to defective absorption of the vitamin. Failure of absorption because of lack of intrinsic factor is the mechanism in classical pernicious anemia and following total gastrectomy. In addition, competition for available B_{12} in the intestine by parasites[18] and bacteria has been implicated as a mechanism by which clinical vitamin B_{12} deficiency may develop.

Failure of vitamin B_{12} absorption due to intestinal disease unrelated to intrinsic factor deficiency has been demonstrated in sprue, regional enteritis, and following massive small bowel resection.

The present study was concerned with vitamin B_{12} absorption using Co^{60}-labeled vitamin B_{12} in 92 subjects. The amount of vitamin B_{12} absorbed by the normal individual was exceedingly small. Even when the administered oral dose was as small as 0.1 μg, an appreciable fraction was excreted (Table III). However, when 0.5 μg or less of the labeled vitamin was administered to normal individuals and to patients with diseases unrelated to pernicious anemia, more than 50 per cent of the administered dose was regularly absorbed. The only exception was a young man convalescing from hepatitis whose defective absorption of vitamin B_{12} remains unexplained but may be related to the Ascaris infestation he was demonstrated to have. When more than 0.5 μg was administered to normal individuals, the per cent of fecal excretion was usually in excess of 50 per cent.

When 0.5 μg or less of Co^{60}-labeled vitamin B_{12} was given to patients with pernicious anemia, more than 60 per cent was excreted in the feces. In addition, defective B_{12} absorption was demonstrated in patients after total gastrectomy and after resection of a major portion of the small intestine and in patients with sprue, regional enteritis, and jejunal diverticulosis.

Our experience, as well as that of others[3,5,6,7,9,11,12,13] establishes the reliability of the radioactive vitamin B_{12} tracer technique as a method to demonstrate impaired absorption of vitamin B_{12}. Measurement of the fecal excretion, the hepatic uptake, or the urinary excretion by the Schilling technique has proved to be satisfactory. The simplicity and speed of the Schilling method make it most adaptable for routine diagnostic use. An important advantage of the radioactive techniques is that absorption defects can be recognized at a time when vitamin B_{12} deficiency is not present. The greatest use of these procedures is in the diagnosis of pernicious anemia in patients who are in remission because of prior therapy. The extensive use of multivitamin and hematinic preparations containing vitamin B_{12}, intrinsic factor, and folic acid has made this an important clinical problem[19] for which the radioactive tracer techniques provide a solution.

Of special interest has been the demonstration of defective vitamin B_{12} absorption in patients with lesions of the small intestine. In view of the severely impaired absorption found in patients with sprue, it is surprising that the neuro-

logic abnormalities of subacute combined degeneration are so uncommon in this disorder. Megaloblastic anemias have been described in intestinal disorders.[20,21] In our patients with regional enteritis the impaired B_{12} absorption was not corrected by the addition of intrinsic factor or by intestinal sterilization with antibiotics. These observations indicate that the defective absorption was due to abnormality of the intestinal wall rather than lack of intrinsic factor or bacterial competition. In contrast the B_{12} absorption defect of a patient with multiple jejunal diverticula disappeared following the administration of antibiotics. In this case vitamin B_{12} presumably was taken up by bacteria growing in the diverticula. Other evidence supporting this interpretation is provided by the experimental studies of Cameron, Watson, and Witts,[22] and the clinical reports of Suirala and Kaipainen.[23] The latter described 2 patients with megaloblastic anemia and subacute combined degeneration secondary to postoperative blind loops in the small intestine. Both had prompt neurologic and hematologic remissions when treated with antibiotics. In addition, Halsted and his associates[11] described 3 patients with intestinal anastamoses and stasis of intestinal contents whose absorption of radioactive vitamin B_{12} improved following the administration of an antibiotic. A similar patient described by Doscherholmen and Hagen[10] failed to show improved B_{12} absorption following antibiotic therapy. The failure may have been due to inadequate sterilization.

It is of interest that impaired absorption of vitamin B_{12} was demonstrated in 2 patients who had had a major portion of the small bowel resected. The absorption defect was not corrected by intrinsic factor or antibiotics.

Differential Diagnosis of Vitamin B_{12} Deficiency States.—Several new techniques have now been adequately tested to establish their usefulness in the differential diagnosis of vitamin B_{12} deficiency states. In the absence of specific neurologic abnormalities, the differentiation between deficiencies of folic acid and vitamin B_{12} is at times difficult. In this situation the measurement of the vitamin B_{12} concentration in the serum [24-26] may be of pathognomonic significance. For example, in megaloblastic anemia due to dietary inadequacy, this is the only procedure which will distinguish between folic acid and vitamin B_{12} deficiency. The "vitamin B_{12} saturation" test has not been useful in distinguishing between normal and vitamin B_{12} deficient states.[27,28]

Since most vitamin B_{12} deficiency states are caused by defective absorption, the most important diagnostic procedures are those which identify and delineate absorption defects. The radioactive vitamin B_{12} tracer studies, when properly carried out, will demonstrate impaired absorption. When these tests are repeated under varying conditions, the nature and mechanism of the defective absorption may be clarified. When defective vitamin B_{12} absorption is due to deficiency of intrinsic factor, as in pernicious anemia or following total gastrectomy, the administration of intrinsic factor will correct the absorption defect. Intrinsic factor will not correct the defective absorption due to other mechanisms. When the absorption defect is due to competition for available B_{12} by intestinal bacteria or parasites, removal of the competing organism results in improved absorption. On the other hand, when defective absorption is a result of disease or inadequacy of the intestinal mucosa, the defect cannot be corrected by these

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procedures. Table VII illustrates how these tests were utilized in studying impaired vitamin B_{12} absorption.

SUMMARY

Over 100 studies of vitamin B_{12} absorption were performed in 92 subjects using vitamin B_{12} labeled with radioactive cobalt. Impaired absorption of vitamin B_{12} from the gastrointestinal tract was observed in patients with pernicious anemia, sprue, regional ileitis, jejunal diverticulosis, and in patients after total gastrectomy or after resection of large portions of the small intestine.

Administration of intrinsic factor preparations corrected the absorption defect in pernicious anemia and after total gastrectomy, but was without effect in the other disorders. Administration of an antibiotic improved the absorption of vitamin B_{12} in a patient with jejunal diverticulosis presumably by eliminating bacterial competition for vitamin B_{12}.

The use of radioactive vitamin B_{12} provides a simple and useful clinical test which has its greatest value in the recognition of pernicious anemia in patients who are in remission as a result of previous therapy.

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CENTRAL RETINAL VEIN OCCLUSION IN JUVENILE DIABETES

Case Report With Consideration of the Pathogenic Relationship Between Diabetic Retinopathy and Retinal Vein Occlusion

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(Received for publication Oct. 21, 1955.)

OCCLUSION of the central retinal vein is a tragic condition because, in approximately 75 per cent of the cases, it leads to sudden and persistent loss of vision of the affected eye.[1]

This clinical entity occurs far more often in old age groups, with the peak of incidence in the seventh decade, yet some cases have also been reported in young adults. Even though detailed medical data are omitted from most reports concerning central retinal vein occlusion, it is generally accepted that the condition in elderly patients often is related to diabetes as well as to hypertension, syphilis, and other diseases in which extensive vascular lesions occur.[2-5]

In younger patients the co-existence of central retinal vein occlusion and diabetes has not been reported. The majority of such cases seems to occur during the course of blood dyscrasias with pronounced thrombotic tendency and of infections which may be general, such as influenza and tuberculosis, or local such as facial erysipelas, paranasal sinusitis, and ophthalmic zoster.[6-8] Because of increased longevity, juvenile diabetics* have become particularly prone to vascular degeneration; and it might therefore be supposed that the occurrence of central retinal vein occlusion would be observed in them. A purpose of this report is to emphasize the presence of central retinal vein occlusion in juvenile diabetics, exemplified by our recognition during a period of only six months of three such cases in young male diabetics (ages 15, 25, and 37 years; duration of diabetes, respectively, 12, 18, and 26 years) and one case in a young female diabetic during pregnancy (age 22 years, duration of diabetes, 11 years).

A careful study of retinal vein occlusion may prove fruitful also in revealing factors which may be important in the development of diabetic retinopathy. This is due to the fact that both conditions produce similar ophthalmoscopic and pathoanatomical features, as already emphasized earlier by Ballantyne,[5,9] Michaelson and Campbell,[10] and Becker and Post.[11]

This study was supported by the Diabetic Fund of Boston and the Massachusetts Lions Eye Research Fund.

*This term is used to describe diabetics of any age, in whom the onset of diabetes occurred at 15.0 years of age or under.

It should be remembered that the collective terms generally in use, retinal "arteries" and retinal "veins," are misleading since by histologic definition these vessels are arterioles and venules[5,12] and by pathophysiologic response behave as such.[13-16] The realization of the latter fact in particular and the results gained from our in vivo investigations of the microscopic reactions of the small blood vessels of the bulbar conjunctiva in young diabetics[17-22] strongly suggest that the characteristic venous retinal changes and their underlying cause in the young diabetic need to be reinterpreted. When this is done, a close pathogenic relationship appears to exist between the development of diabetic retinopathy and retinal vein occlusion in these young patients. Because several unique features in one of our patients (Case 19762) exemplify this concept and because this patient is the youngest (15 years) with central retinal vein occlusion whom we can find reported in the literature, the case history is presented and discussed in detail.

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CASE REPORT

The patient was a 15-year-old boy with diabetes of 12 years' duration. The paternal uncle had diabetes. Past history was not remarkable. At 3 years of age there was sudden onset of thirst and the diagnosis of diabetes was established during an attack of pertussis. He was placed on a growth diet and 20 units of protamine zinc insulin daily. The diabetes was never adequately controlled. The loss of his mother added to the difficulties of diabetic control. In the eighth year of diabetes, he had three attacks of diabetic coma and one of severe ketoacidosis. Additional attacks of acidosis occurred in the seventh and twelfth year of diabetes. Furthermore he was obese and had retardation of growth and development, hepatomegaly, and many convulsive seizures which were interpreted as insulin reactions. In the tenth year of diabetes he was transferred to NPH insulin.

The twelfth year of diabetes was again characterized by extremely poor control. An attack of acidosis and two severe insulin reactions necessitated hospitalization and preceded the onset of central retinal vein occlusion. Three weeks prior to this admission to the hospital, he noted blurred vision in the left eye. This rapidly progressed to almost complete loss of vision.

Upon admission to the New England Deaconess Hospital the following data were found: blood sugar, 86 mg. per 100 ml.; nonprotein nitrogen, 45 mg. per 100 ml.; cholesterol, 205 mg. per 100 ml.; prothrombin activity, 45 per cent of normal; clotting time, 21 minutes (Dicumarol therapy had been started on an outpatient basis). There was no proteinuria, no edema, no neuropathy, and the blood pressure was 120/60. The patient was seen by an ophthalmologic consultant, Dr. William P. Beetham, who reported early diabetic retinopathy in the right eye and thrombosis of the central retinal vein in the left eye. There had been five examinations of the retina prior to this ophthalmoscopic examination, all of which were normal. The latest one was *five months prior* to this admission.

Ophthalmologic Report on Admission, Oct. 2, 1952.—

"With the right eye he obtains an acuity of 6/6. The eye moves properly in all directions. The ocular media are clear. A moderate number of punctate hemorrhages in the fundus are found and increased light reflexes are present suggesting a few very small areas of edema in the retina. The retinal veins are markedly distended, very dark and fairly irregular (Grade +4).

"Visual acuity with the left eye is recorded as "the ability to count fingers at 1 or 2 feet." The ocular media are clear. The optic disc is markedly blurred due to edema and exudation There are many hemorrhages, mostly nerve-fiber layer in type, extending from the disc in all directions. There is much exudation in the retina particularly around the periphery. The retinal veins are very dark and markedly distended. The picture is interpreted as a thrombosis in the central retinal vein." (W.P.B.)

Observation of the conjunctival vessels with Knisely's technique* by one of us (J.D.) was made on his third day of admission and showed marked "Vascular Pattern-Change I" characterized by slight constriction of the arterioles, marked distension of the larger venules with an ateriolar/venular diameter ratio of 1:7-1:8, marked aggregation of the blood cells, considerable slowing of blood flow with stasis even in larger venules (30 to 90 microns in diameter) and massive exudation.

Conjunctival vessel examination of both eyes:

Arterioles: The terminal arterioles measure approximately 8 to 16 microns and are moderately narrowed. The flow of blood is visible and aggregates of blood cells which measure approximately 18 microns can be seen plugging the tips of the arterioles before they are squeezed through the capillaries (Grade 3). There is no visible vasomotion.

Capillaries: Approximately 50 per cent are elongated with tortuosities and angularities in the venous parts (Grade 2). Due to the marked venular distension the venous parts in some of the capillaries are funnel-shaped, expanded in the utmost venous end. The aggregates of erythrocytes are slowly flowing or static and in some smaller venules (12 to 30 microns) the aggregates have settled and form microthrombosis.

Venules: All venules are markedly distended and show numerous sausage-shaped dilatations. The arteriolar/venular diameter ratio measures approximately 1:7-1:8. The flow of blood is considerably reduced even in the larger venules (30 to 90 microns in diameter). The conjunctival tissue is very blurred, + + edema (Grade 2).

Vascular response: "Vascular Pattern-Change I"

Grading:	Vascular changes:	2
	Perivascular changes:	2
	Intravascular changes:	3

[18]

(Scales 0-3)

The patient was discharged from the hospital on Dicumarol therapy, but no beneficial effect was obtained. Ophthalmoscopic examination showed no definite change in the retina after the onset of the central retinal vein occlusion. The patient complained of pain in the left eye a month after onset of the thrombosis and cauterization was performed six weeks after the initial hospitalization. The pain persisted, however, and enucleation was finally performed four months later.

Follow-up approximately three years after the onset of the central retinal vein occlusion showed an 18-year-old boy with diabetes of 15 years' duration. He was in good health and had no complaints. Blood sugar was 104 mg. per 100 ml.; urine sugar, 0.4 per cent; blood pressure, 120/80; no proteinuria; no signs of neuropathy. Paper electrophoresis of the serum proteins showed an elevation of the beta lipoproteins, but no unique changes in either the over-all protein pattern or the protein-bound carbohydrate. Ophthalmoscopy of the right eye showed an unchanged picture of retinopathy with the characteristics common in juvenile patients with long-term diabetes. Conjunctival vessel examination showed a regression of the earlier finding of "Vascular Pattern-Change I" to a normal pattern with an arteriolar/venular diameter ratio of 1:3-1:2.

Ophthalmoscopic Report, Aug. 19, 1955.—

"With his right eye he obtains an acuity of 6/5 without glass correction. The ocular media are clear, and the optic disc is normal. There is possibly some 40 to 50 small microaneurysms scattered here and there throughout the fundus. In the superior portion of the fundus is a small new loop of vessels which suggests a beginning of proliferating retinopathy. In addition to this the retinal veins are very large, distended, and dark (Grade +3). The arteries show increased light reflexes and possibly slight thickening of the walls. There are no exudates present.

"Left eye: Prosthesis." (W.P.B.)

***Normal findings in 70 healthy children.[21] The configuration of all vessels is smooth. The ratio between the diameter of the arteriole and that of the accompanying venule is constant, being 1:3-1:2. There is no perivascular edema. The rate of blood flow in arterioles and venules is so rapid that no cellular detail can be observed. No intravascular aggregates of erythrocytes are present.**

Conjunctival vessel examination:

Arterioles: The arterioles are slightly narrowed along the whole course and in some few places consistent focal irregularities in the configuration can be seen suggesting arteriolosclerosis. There is no visible aggregation and no plugging; no visible vasomotion.

Capillaries: The capillary network is markedly irregular and approximately 50 per cent of the venous parts showed elongation with an angular, tortuous course (Grade 2). There is definite evidence of new formation of small vessels. Small soft aggregates are seen occasionally which measure 9 to 12 microns (Grade 1 to 2). The rate of flow is slightly reduced.

Venules: The venules are not distended and the arteriolar/venular diameter ratio measure approximately 1:2-1:3. The smaller venules show an elongated course with some tortuosities. There is aggregation and slightly reduced flow of blood. The tissue is not edematous and no "hyaline-like infiltration" in the tissue can be seen (Grade O).

Grading:
Vascular response: normal (changed)
Vascular changes: 2 (unchanged)
Perivascular change: 0 (changed)
Intravascular changes: 1-2 (changed)
(Scales 0-3)

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COMMENT

This case is of unusual interest for three reasons. First, because of the young age, 15 years, at which this boy developed central retinal vein occlusion, a condition which occurs most commonly in the seventh decade; second, because of the probable significance of the immediate time-relationship with which he developed nonproliferating diabetic retinopathy in one eye and central vein occlusion in the other; and third, because an unusual opportunity was afforded to make detailed observations of the vascular reactions and the morphologic changes in two different tissues simultaneously, the retina and the bulbar conjunctiva (representing the subcutaneous tissue), at the time of the lesion and subsequently at a three-year follow-up.

DISCUSSION

At this clinic, effort has been made to evaluate the vascular changes taking place in the bulbar conjunctiva of young diabetic patients—the only site of the body in which detailed in vivo microscopic observations of the smallest radicals of the vascular peripheral bed can be made.[17-22] This study has demonstrated that at any given time this vascular bed in most young diabetics shows a combination of functional and morphologic changes which predominantly are venous in origin. Serial observations made a distinction possible between the two types of changes, and it was shown that the functional alterations consisted of a set of pathophysiologic vasomotor responses maintained by some stimuli in the diabetic metabolic disturbance.[20] These responses formed two main pattern deviations from that of "healthy" individuals which varied quantitatively in degree from time to time. By far the greatest number of diabetics showed the "Vascular Pattern-Change I." This is characterized by a slight and inconsistent narrowing of the terminal arterioles, a pronounced loss of tone of the larger venules (arteriolar/venular diameter ratio 1:4-1:10 (normal 1:2-1:3). These caliber changes are accompanied by aggregation of the circulating blood cells, a decreased rate

of blood flow, and an increased permeability of plasma through the venular walls. In some diabetic patients the "Vascular Pattern-Change II" was observed. This is characterized by a marked increase in vascular tone, since the arterioles and venules both are tightly narrowed and many of the true capillaries completely closed. Most of the circulating blood is shunted through some persistently open vascular channels of capillary size from the terminal arterioles direct into the larger venules. The circulating blood often contains resistant aggregates of blood cells which intermittently plug the terminal arterioles. The linear rate of blood flow is considerably reduced and the tissue appears ischemic and edematous. By serial observations and by statistical evaluation of single observations in diabetic children, causative links have been demonstrated between the reversible response changes and the irreversible degenerative changes in the bulbar conjunctiva.[20,21] A statistical relationship was also found between the degree of degenerative changes and the duration of diabetes.[21] It therefore is reasonable to suppose that the pathophysiologic vasomotor responses lead to the degenerative changes in the conjunctiva and that similar pathophysiologic responses elsewhere in the body over a period of years lead to the permanent clinical microangiopathy in diabetes.

In the case presented, the venules of the bulbar conjunctiva at the onset of the central venous occlusion were markedly distended, but not so at the time of the follow-up. This fact demonstrates the venular distension in the bulbar conjunctiva at the onset of central retinal vein occlusion as a reversible vascular response, since the vascular system of the bulbar conjunctiva is anatomically unrelated to that of the retina.

In the retina of young diabetics, the most characteristic changes are found in the venous part of the capillaries, in the venules and veins, the latter of which show marked similarities to those observed in the bulbar conjunctiva.[17] Even though von Michel,[23] Nettleship,[24] and Hirschberg[25] in the last century mentioned the venous retinal changes, it is only in the last two decades and coincidental to the increased longevity in young diabetics that more attention has been drawn to the changes in the configuration of the retinal veins. Ballantyne[5,26] repeatedly stressed the increased fullness, the distension and elongation of the retinal veins as a frequent finding in diabetic retinopathy. Few ophthalmoscopic studies have been made to evaluate the state of the veins early in the diabetic condition and the time relationship between the appearance of distended veins and the "sanguinolent spots" (microaneurysms and small punctate hemorrhages); but Ballantyne,[27,28] Marshall,[29] and Gibson[30] all were impressed by the early appearance of distended veins and their probable significance in the development of capillary microaneurysms. O'Brien and Allen,[31] Gibson and Smith,[32] and Michaelson and Campbell,[10] all described more marked changes in the configuration of the retinal veins such as localized bulges, sausage-shaped dilatations, and "bead-string veins" of young diabetics. Ditzel and Sagild[17] described similar marked venous changes in the bulbar conjunctiva of young diabetics. Jensen[33] emphasized the great difference between the changes taking place in the retina of young diabetics as compared to those in middle-aged and elderly diabetics. In young diabetics the retinal changes were characterized by the marked

venous changes, "sanguinolent spots" and proliferation of new blood vessels, and he designated the retinal condition in these young individuals "phleboretinopathia tarda." Recently, Lundbaek[34] in his study of long-term diabetes statistically confirmed that "phlebopathy" was predominantly a phenomenon in young long-term diabetics. This parallels our finding in the bulbar conjunctiva, in which the venular distension was found statistically more frequent among young diabetics under 35 years of age (48 per cent) than among older diabetics above the age of 55 (6 per cent).[17]

The cause of the caliber changes of the retinal veins is as yet unsettled. Ballantyne[5] commented upon the term "phlebosclerosis" which so often is used as a general description of these changes. By pathoanatomic studies he arrived at the conclusion that this term should be abolished since the majority of the recognizable veins are dilated, *thin-walled* vessels without sclerosis. Ballantyne suggested that the dilatation of the retinal veins might be caused by some obstruction in the course of the main trunk of the central vein, which would be consistent with the fact that diabetes is one of the recognized causes of occlusion of the central retinal vein. However, in most cases he failed to find any histologic sign of such obstruction. Today there is no evidence which disproves the supposition that the venous distension in the retina in the initial stage is a vascular response of reversible nature and due to loss of tone, as in the conjunctiva. This hypothesis is supported by our data from simultaneous observations of the retina and the bulbar conjunctiva in diabetic children, which showed that when a marked distension of the venules occurred in the conjunctiva there was always distension of the retinal veins. The reverse was not true, as is illustrated in the case herein presented.[19] The differences in permanent reversibility of the venular response change are apparently due to differences in the architecture and functional need of the vessels in the retina and in the conjunctiva. The retinal vessels are placed close upon the nerve-tissue, separated only by a thick basement membrane which surrounds the whole vascular tree; and the supply of lymphatics in the retinal tissue is limited. After some years of diabetes, the basement membrane becomes "hyalinized." This may be in response to intermittent exudation through the venular and capillary walls. The conjunctival vessels have no basement membrane; there is a rich network of lymphatics; and the whole conjunctival tissue can act as a pool from which the exudation is absorbed. Therefore, the venular distension in the conjunctiva is reversible for a much longer time than in the retina. Furthermore, the functional need of the conjunctival vessels in a relatively inactive tissue is minimal compared to the need of the retinal vessels which are in a tissue with an extremely high metabolic rate.[35] This implies that while the vascular response to hypoxia in the conjunctiva may only be slight and occurs principally in the venules, similar vascular reactions in the retina will be vigorous and involve not only the venules but also the venous part of the capillaries.

Even though clinically diabetic retinopathy and central retinal vein occlusion are two definitely distinguishable entities, they have, when the processes are once started, many ophthalmoscopic features in common. The onset of the central retinal vein occlusion is sudden, and the time interval from onset to the

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development of the characteristically ophthalmoscopic picture is short. By ophthalmoscopy the first finding is a violent dilatation of the main retinal veins with increase fullness and a strikingly dark color. Some hours later there appears "small round hemorrhages" and small edematous areas scattered all over the fundus. After various time intervals the fundus picture becomes more dominated by flame-shaped hemorrhages, exudates, and exudative coatings around the markedly dilated veins. Occasionally the final stage of a central retinal vein occlusion develops into a typical case of retinitis proliferans.[1]

The onset and progress of diabetic retinopathy in young diabetics is slower than that of central retinal vein occlusion and occurs usually after a history of diabetes of ten years or more. However, the pattern of development from the early into severe stages is somewhat similar to that occasionally seen in cases of central retinal vein occlusion. One first observes some few "sanguinolent spots" (microaneurysms and small punctate hemorrhages) located in the posterior part of the fundus and probably some distended and elongated veins. At a later state of diabetic retinopathy there appear more marked changes in the configuration of the veins, patchy exudates, and occasionally flame-shaped hemorrhages. In some cases of diabetic retinopathy a formation of new vessels protrudes from the surface of the retina out in the vitreous body, forming retinitis proliferans.

The similarities between central retinal vein occlusion and diabetic retinopathy are not confined to the ophthalmoscopic picture, but become even more striking when studied pathoanatomically. Capillary microaneurysms, the charteristic lesion in diabetic retinopathy, have likewise repeatedly been demonstrated in cases of retinal vein occlusion. Becker and Post[11] thus studied histologically 39 cases of retinal vein occlusion with the Hotchkiss method and found capillary microaneurysms in all. They reported that in some cases the microaneurysms were indistinguishable from those observed in diabetes. They also were able to produce microaneurysms as part of a picture closely simulating clinical vein occlusion in man by an experimentally produced thrombus in the retinal veins of cats. Ashton[37] confirmed the finding of capillary microaneurysms in cases of retinal vein occlusion, and found them likewise in smaller numbers in various other clinical conditions of local and generalized nature. He concluded that even though diabetes remained as the condition in which microaneurysms were found most frequently, in their greatest numbers and most advanced forms, their existence in other conditions is probably related to the severity and chronicity of their causative factors. Pathoanatomic studies have shown in both diabetic retinopathy and central retinal vein occlusion, besides capillary microaneurysms, a distortion of the capillary network, a new formation of vessels either at the surface of the retina or into the vitreous body and dilated venules with evidence of fatty degeneration.[11,36,37,38]

The mechanism of formation of microaneurysms in retinal vein occlusion appears fairly clear. In this condition a sudden onset of stasis occurs which might be brought about by various factors (Fig. 1). The stasis causes anoxia and undernutrition of the venular and capillary walls, leading to focal mural degenerative changes of the basement membrane and aneurysm formation.

The production of capillary microaneurysms in diabetes may be explained in a similar way. In this disease various degrees of venular distensions occur intermittently for years as part of a pathophysiologic vasomotor reaction in the small blood vessels.[17-22] Associated with this change is occasional narrowing of the terminal arterioles. Both caliber changes tend to slow down the linear rate of blood flow, particularly in the venous circulation. Changes in the normal plasma protein pattern of diabetic patients leads to aggregation of circulating blood cells which, in addition to venular distension, is likewise a factor in slowing down the rate of flow.[17,39] When these factors coincide, stasis occurs and clumps of aggregated blood cells settle and form "pseudo-thrombosis" in the venous part of the capillaries and smaller venules of the retina. Even under optimal circulatory conditions, the venous parts of the capillaries and the smaller venules are the places with the slowest rate of blood flow. The stasis is particularly marked in the more dense and relative circulatory-dependent capillary network of the inner nuclear layer, and in accordance it is here that the capillary microaneurysms are mostly concentrated in diabetic patients.[10,40] The stasis, anoxia, and engorgement lead to focal mural degenerative changes in the basement membrane and microaneurysm formation.

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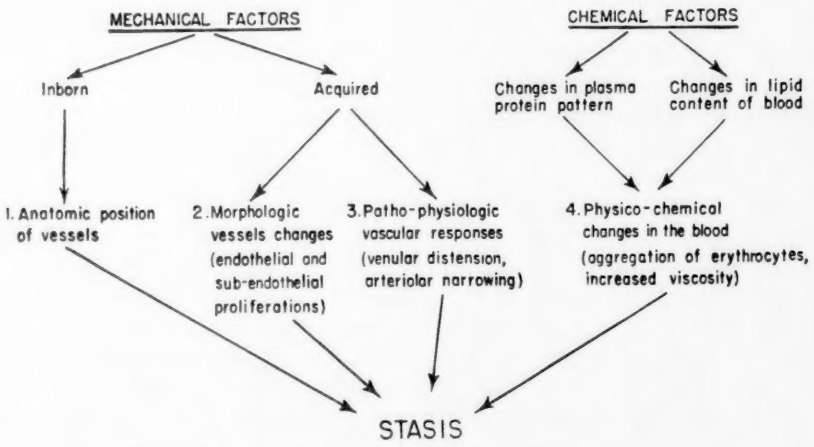
MECHANICAL FACTORS
CHEMICAL FACTORS
Inborn
Acquired
Changes in plasma protein pattern
Changes in lipid content of blood
1. Anatomic position of vessels
2. Morphologic vessels changes (endothelial and sub-endothelial proliferations)
3. Patho-physiologic vascular responses (venular distension, arteriolar narrowing)
4. Physico-chemical changes in the blood (aggregation of erythrocytes, increased viscosity)
STASIS

Fig. 1.—Factors leading to stasis in the venous retinal circulation.

Thus, it appears that the diabetic retinopathy and retinal vein occlusion in young diabetics has stasis in the venous retinal circulation as a common pathogenic factor. This may explain the occurrence of central retinal vein occlusion in young diabetics. The stasis in young diabetics is brought about by several factors of which the distension of the venules and the intravascular aggregation of the blood cells are of particular importance (Fig. 1). Even though no conclusion can be drawn from a single case, the development of retinopathy in one eye in near time-relationship to the formation of central retinal vein occlusion in the other (case reported above) tends to emphasize a chronic condition of stasis in the venous retinal circulation as an important factor in the development of diabetic retinopathy.

SUMMARY

The occurrence of central retinal vein occlusion in juvenile diabetics is emphasized.

Based on an unusual case report of a 15-year-old diabetic boy in whom diabetic retinopathy developed in one eye in immediate time-relationship of central vein occlusion in the other, the pathogenic relationship between these two conditions is discussed. The mechanism of the production of stasis in the venous retinal circulation in young diabetic individuals and in central retinal vein occlusion is outlined. A chronic condition of stasis in young diabetics appears to be brought about mainly by a distension of the venules as part of a pathophysiologic vasomotor reaction and intravascular aggregation of the red blood cells. It is suggested that a condition of stasis in the venous retinal circulation is a common pathogenic factor in the development of retinopathy and retinal vein thrombosis, and that this may explain the occurrence of central retinal vein occlusion in young diabetics.

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HERITABLE DISORDERS OF CONNECTIVE TISSUE

VI. Pseudoxanthoma Elasticum

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(Received for publication Dec. 5, 1955.)

HISTORICAL NOTE

THE first description of the skin changes and the first autopsy report were provided by Balzer[1] in 1886. Because of the yellow and elevated appearance of the skin lesions, the disorder was grouped with the xanthomatoses by Balzer and by Chauffard.[10] The disease was identified as a separate and nonxanthomatous entity by Darier[14] in 1896.

In 1889 Chauffard,* at a meeting of the Société Médicale des Hôpitaux in Paris described a patient destined to occupy a prominent role in the history of this disease. His case was separately reported, during the next fifteen years, by Besnier and Doyon[6]; by Darier,[14] who established the histopathology and offered the name *pseudoxanthoma elasticum* with the alternative *elastorrhexis;* and by Hallopeau and Laffitte,[31] who described dramatic changes in the fundus oculi. The patient's well-documented story is of further interest because it demonstrates the typical features of the syndrome from which he suffered: changes in the skin, repeated massive gastrointestinal hemorrhages, weak peripheral pulses, and failing vision. Chauffard's description[10] follows†:

> This is a man of thirty-five years. . . . At twenty-four years of age, while doing his military service in New Caledonia, he suffered a large hematemesis. This accident repeated itself several times (at ages twenty-six, thirty-one and thirty-three). This summer he was admitted to the Hôtel Dieu for a hematemesis.
>
> In 1880 L. was discharged and returned to France; and it was shortly afterward, he states, when he noted the beginning of his skin affection. . . . The xanthomatous eruption is comprised of a series of evolving groups, perfectly symmetrical and confined exclusively to the several flexoral folds, that is, base of the neck, the two axillary creases, the folds of

Based on work supported in part by the Daland Fund of the American Philosophical Society and in part by a grant-in-aid from the National Institutes of Health, U.S.P.H.S.

Reprints of this entire series of articles, appearing in successive issues of the Journal, will be available through the publishers in book form following appearance of the last installment.—Editor.

*Anatole Chauffard, an internist, is better known for his discovery (with Minkowski) of congenital hemolytic icterus (1900) and of the increased fragility of the erythrocytes in this condition (1907).

†Translation mine.

the elbows, the anterior abdominal wall, especially just below the umbilicus, the two inguinal triangles, the inferior aspect of the penis, around the anus, the two popliteal fossae. . . . The center of the group is formed by an almost confluent agglomeration of intradermal placques, soft to the touch, projecting to some extent like papules, separated by small folds of skin. Their coloration is rather pale, resembling that of fresh butter or yellow chamois; the size of the largest placque is scarcely greater than that of a pea. . . . If one retracts both lips, one sees that the mucosa of the inner aspect is involved. It demonstrates a cluster of small, yellowish intramucosal nodules, resting on a richly vascular background traversed by numerous dilated and tortuous capillaries. . . . In February there developed an unusual phenomenon of which there is today scarcely any trace remaining. The peripheral zone of the eruptive groups in the skin were traversed by rather large, violaceous rose networks which were not elevated and formed a congestive halo around the yellow placques. . . . Today traces of this perinodular hyperemia remain only in the pectoral regions, on the anterior extension of the axillary groups. . . .

The pulse is feeble and compressible and gives with the sphygmometer of Verdin a tension of 650, rather than of 750, the average normal figure.

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In August, 1896, at the Third International Dermatologic Congress in London, Darier[14] reported histologic studies on the skin of Chauffard's patient. By 1903, this patient had developed amblyopia; and Hallopeau and Laffitte[31] reported that there was "chorioretinitis of the central region, involving the macula, with secondary atrophy of the optic disc."

Although Hallopeau and Laffitte in 1903 speculated that there might be some connection between the changes in the skin and those in the fundus oculi of Chauffard's patient, it was not until 1929 that the relationship of angioid streaks and pseudoxanthoma elasticum was established by Ester Grönblad,[26] an ophthalmologist, and James Strandberg,[64] a dermatologist, both of Stockholm. Angioid streaks had been described by Doyne[16] in 1889, and the name was assigned by Knapp[41] in 1892. Knapp thought angioid streaks to have a vascular basis. Their origin as a result of crazing of Brück's membrane was first suggested by Kofler[42] in 1917.

Involvement of the peripheral arteries in this syndrome and the physiologic consequences thereof have been studied in the last twenty years by Carlborg,[9] Van Embden Andres,[76] Scheie and Freeman,[58] Urbach and Wolfram,[75] Prick,[38,55] Guenther,[27] and Wolff and his associates.[81] Gastrointestinal hemorrhage was emphasized by several of these authors and particularly by Revell and Carey[56] in 1948. Evidence that this disease may be an abnormality of collagen fibers rather than elastic fibers can be attributed largely to Hannay,[32] who used standard histologic techniques, and to Tunbridge and collaborators,[74] who used electron microscopy.

Pseudoxanthoma elasticum is an objectionable name for this syndrome since it refers only to its cutaneous aspect, since it perpetuates the possibility of confusion with the xanthomatoses, and since it conveys the notion that elastic tissue is unequivocally the defective element. Unfortunately, the only eponym which has been applied to this syndrome at all frequently, Grönblad-Stranberg, is not easily remembered or spoken and has not attained wide use. "PXE" is the abbreviation which will be used frequently in this presentation to refer to the entire syndrome.

CLINICAL MANIFESTATIONS

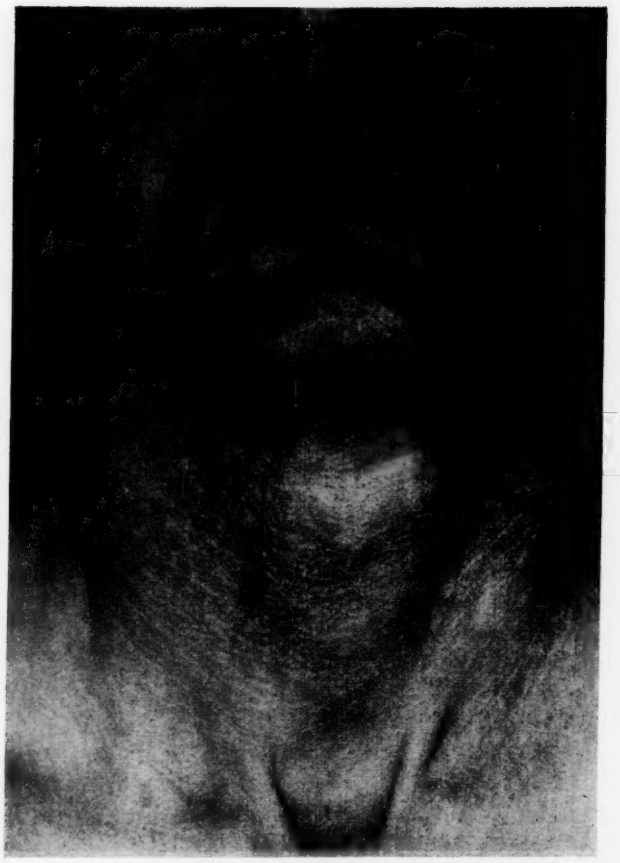
Clinical expression of PXE is found mainly in three areas: The skin, the eye, and the cardiovascular system. Because of the widespread involvement of the muscular arteries, hemorrhagic symptoms referable to virtually every organ system may occur. The following descriptions are based in part on sixteen cases observed at this hospital.

The changes in the skin (Figs. 1,*A* and 2,*A*) are often not recognizable clinically before the second decade of life or later. The face, neck, axillary folds, cubital areas, inguinal folds, and periumbilical area are particularly prone to involvement. The skin becomes thickened and grooved like coarse-grained Moroccan leather. The areas between the grooves, diamond-shaped, rectangular, and polygonal, are elevated and yellowish in color. *Cutis rhomboidalis nuchae* and *la peau citréine*, although terms used for conditions distinct from PXE, would often be appropriate for the changes seen in these patients.[67] The skin in the involved areas becomes lax, redundant, and relatively inelastic. In girls, and the female is more often affected by this disorder, the cosmetically undesirable changes in the skin, especially that of the neck, are often occasion for consulting medical advice. The soft palate often shows changes grossly and histologically identical to those in the skin.[23] At times the mucosa of the rectum and vagina is affected.[9] In some patients the cutaneous changes are exceedingly mild despite advanced ocular and arterial changes (Fig. 2). Van Embden Andres[76] described four patients with only minimal clinical but typical histologic changes in the skin. In two other cases of his, there were no clinically detectable changes in the skin yet positive findings on biopsy.

The characteristic changes in the eye are demonstrated by fundoscopic examination and consist of angioid streaking of the fundus (Fig. 1,*B*). These streaks are brownish or gray in coloration and are four or five times wider than veins but resemble vessels in the manner in which they course over the fundus. Proliferative changes occur, with the angioid streaks as points of origin. Hemorrhages from the retinal vessels occur both with and without trauma to the eye and are followed by organization. These retinal changes result in loss of vision, which is usually only partial, yet very severe. White or yellowish dots referred to as colloid bodies, or *Drüsen*, are described[81] and were present in the vicinity of the discs in the patient whose skin changes are demonstrated in Fig. 2. The angioid streaks are by no means necessarily present at birth; actually, like the skin changes, they usually develop in the second decade of life or later. Whether trauma plays any contributory role in their pathogenesis is unclear.

It is important to realize that although angioid streaks are the ocular hallmark of PXE, not infrequently only a less specific central chorioretinitis is present.[5,76] This may have been the case with Chauffard's famous patient.[31] Like the hemorrhages, the central chorioretinitis is a grave threat to vision because of involvement of the macular areas.

Clinically the arterial involvement is expressed by pulse changes and symptoms of arterial insufficiency in the extremities, by x-ray evidence of premature medial calcification of peripheral arteries, by symptoms of coronary insufficiency, by hemorrhage in one or more of many different areas, and by hypertension.



A.

B.

Fig. 1, *A* and *B*. *(For legend see opposite page.)*

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Weakness or absence of pulses in the extremities is a frequent finding. Fatigability or frank intermittent claudication may occur in the legs. The development of these manifestations by the third decade or earlier and the involvement of the arms as well as the legs aids in the differentiation of these changes from those of ordinary arteriosclerosis. Figs. 1,*C* and 1,*D* give an example of arterial calcification which began to develop at least as early as the latter part of the third decade of life. Calcification as early as the age of 9 years has been described[81]; in this child, intermittent claudication, loss of pulsations in the distal arteries of the limbs, calcification of the arteries, and repeated attacks of melena (see below) were present. A brother, 25 years old, had similar symptoms.

C. *D.*

Fig. 1.—C. T. (582989), a 32-year-old man. *A*, The skin is lax, rigged, and grooved with a yellowish tint. *B*, Angioid streaks and proliferative changes in fundus oculi, *C*, Calcification of deep femoral artery (photograph retouched). *D*, Calcification of posterior tibial artery (photograph retouched). *E*, Histologic changes in the skin. Elastic tissue stain. (×50.) *F*, Same. (×125.) The skin of the neck, axillae, and groin is involved. Both second toes have a congenital flexion deformity ("hammer toe"). Beginning at the age of 30 years, the patient has had a total of about ten massive gastrointestinal hemorrhages necessitating hospitalization and transfusion. No bleeding site has ever been identified. X-ray of the lungs reveals peculiar nodular densities diffusely distributed throughout both lung fields.

E.

F.

Fig. 1. *E* and *F*. *(For legend see page 267.)*

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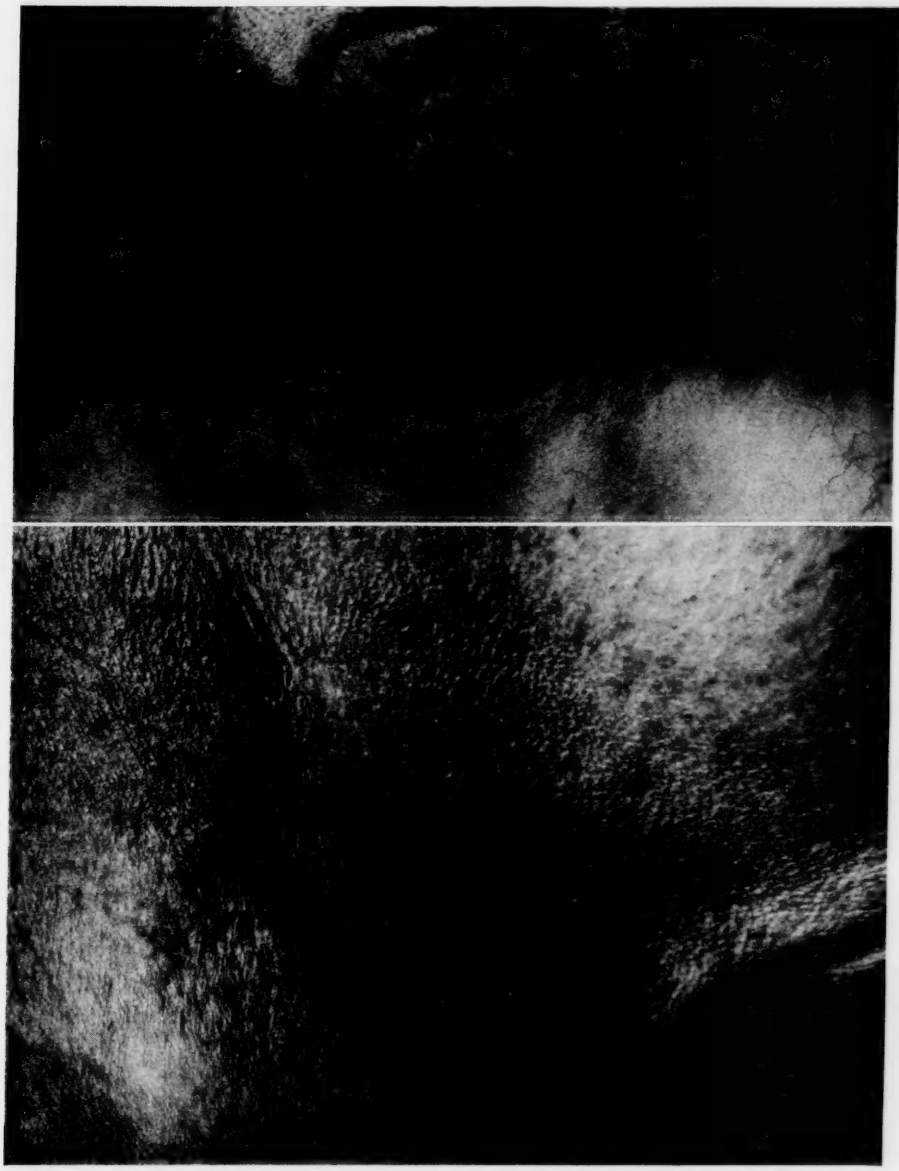
A.



B.

Fig. 2.—P. J. G. (J.H.H. 721600), 45 years old, had a severe gastrointestinal hemorrhage at the age of 34 years. No basis was discovered and there was no recurrence. He was told at that time that he had hemorrhage in the right eye. For several years, especially in winter, he noted cramping and fatigability of the legs. At the age of 44 there was onset of progressive failure of vision. There are no similar abnormalities in the family. Examination revealed only minimal changes in the skin of the neck (*A* and *B*). The skin would have been passed as normal were it not for the rest of the clinical picture. The skin elsewhere was normal except possibly for slightly increased looseness in flexure areas. Both fundi showed large areas of old hemorrhage and fibrosis in each macular area, typical angioid streaks and hyaline bodies near the optic discs. No pulses were palpable in the legs below the femorals. Blood pressure and electrocardiogram were normal. The aorta was moderately tortuous, and serum cholesterol was 335 mg. per cent. (Patient seen through courtesy of Dr. J. R. Krevans.)

Angina pectoris probably occurs more frequently than would be expected in the age groups concerned.

Hemorrhages constitute the major medical problem in most cases of PXE which come to the attention of the internist. Gastrointestinal hemorrhage is common[37] and may be fatal.[29,71] It may occur from a lesion such as peptic ulcer or hiatus hernia, which per se can produce hemorrhage, but in most cases of PXE the source of bleeding is not evident on clinical study. In cases of peptic ulcer, the arterial disease plays a strong contributory role to hemorrhages, similar to that of arteriosclerosis and primary amyloid disease. In my own experience, gastrointestinal bleeding in PXE has occurred as early as 18 years of age. In cases of gastrointestinal hemorrhage, the physician should almost automatically look for the skin changes of this syndrome just as one should look for Kayser-Fleischer rings in patients with liver disease, and for cutaneous telangiectasia in these same patients with gastrointestinal hemorrhage. Some patients visit many different clinics seeking the cause of bleeding. Some have repeated abdominal explorations and repair of some lesion, such as hiatus hernia, which may or may not be incidental.

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In addition to gastrointestinal bleeding, the types of hemorrhage by location include subarachnoid, retinal, renal, uterine,[76] bladder, and nasal. Spontaneous hemarthroses occur.[76] Excessive bleeding from cuts of the skin does not seem to be a problem, although hemorrhages in the skin lesions have been described.[21,47] Foerster's patient[20] sought medical advice because of purpura on the legs, and later on the left forearm. At the age of 16 years, one of the patients in my series (R.E.H., J.H.H. 193470) had a severe illness diagnosed as "black (hemorrhagic) measles." It is possible that the connective tissue disease was responsible for the hemorrhagic manifestations of the measles. Subarachnoid hemorrhage is commonly a cause of death.

The incidence of hypertension is probably high enough to make it worthy of consideration as a genuine component of this disease syndrome. It may be the result of vascular disease, of the PXE type, in the renal vessels, but this is pure speculation. The occurrence of hypertension is unfortunate because of its aggravating influence on the tendency to hemorrhage. In one patient,[15] 29 years old, intracranial "berry" aneurysm occurred in association with skin changes and angioid streaks. Another patient (E.W., J.H.H. 69818), seen in the past in this hospital and twice reported,[34,56] has since died of cerebral hemorrhage at the age of 43 years. Severe hypertension and pronounced albuminuria were persistently present in the last few years of life.

Calcification in peripheral arteries (both arms and legs) has been determined radiologically by a number of observers, including Sanbacka-Holström,[57] Zentmayer,[84] Silvers,[60] Silvers and Wolff,[61] Carlborg,[9] Scheie,[58] and Wolff.[81] Calcification, probably also of vascular location, is sometimes demonstrated in the choroid plexus[76] by skull x-ray. It was demonstrated in the siphon of the internal carotid artery in a 30-year-old patient of this series and in Zentmayer's case.[84] Hypercholesterolemia is not a necessary factor in the premature vascular change, although its presence probably exaggerates pathologic alterations.

Dilatation of the aorta has been remarked on in several of the cases. This

was the case, for instance, in Joffe's 30-year-old patient[35] and in the 35-year-old, normotensive patient of Marchionini and Turgut.[48] Whether this finding bears a direct relationship to the fundamental defect is unclear. Case 9 of Carlborg[9] demonstrated marked dilatation (phlebectasia) of the jugular veins.

Psychiatric disorders seem to occur with abnormally high frequency in these patients. Whether these can be explained on the basis of cerebral vascular changes is difficult to state. Certainly the high incidence of neurologic abnormalities is attributable to the vascular disease and hypertension. The nature of the neurologic abnormalities will not be discussed in detail because they are highly variable, yet per se not unlike what one customarily encounters with advanced arteriosclerosis and/or hypertension. The unusual feature is the relatively early age at which the neurologic accidents and deterioration occur.

PATHOLOGY

In the skin, the characteristic changes occur in the deeper and middle zones of the corium (Fig. 1,*E*). Large aggregations of material with the staining property of elastic fibers dominate the field. This material is granular for the most part, but in places rodlike structures more closely resembling fragmented collagen bundles are seen. Tuberculoid areas with giant cells[70,79] occur in the area of degeneration (see Fig. 2-C in ref. 7). Calcification of the degenerated material occurs to a pronounced degree. This was established by Finnerud and Nomland,[19] using von Kossa's stain, and by Lobitz and Osterberg,[45] using microincineration. Actual bone formation is claimed.[3]

Most histologic studies of the eye[8,22,29,40,77] have shown basophilia and tears in the lamina elastica of Brück's membrane; Benedict[4] and Law[43] failed to find these, however. Most observers, furthermore, have found advanced sclerotic changes in the choroidal vessels. When tears are present in Brück's membrane, scar tissue tends to occupy the breaks or extend through beneath the pigment epithelium.[22] The breaks are probably the site of the streaks seen on fundoscopic examination. Basophilia of the lamina elastica is encountered not infrequently in the eyes of older individuals; it occurs more regularly and at a younger age in PXE. Descemet's membrane of the cornea has chemical, physical, and tinctorial resemblances to the lamina elastica of Brück's membrane. However, clinical or histologic evidence of involvement of the cornea has apparently not been observed in PXE.

Gross and histologic studies of the cardiovascular system are few. In the original case of Balzer,[1] whitish thickening of the endocardium of the right atrium was described, as well as placques of the same description on the pericardium and on the ventricular endocardium. Histologically, degeneration, thought to involve elastic elements, was demonstrated at these sites and in the walls of the pulmonary alveoli. (I have observed identical findings in one of two autopsied cases described in detail below.) Two other necropsy cases have been reported in detail in the literature. In Prick's case[38,55] the patient had hypertension and died at the age of 45 years of a cerebrovascular accident. Histologic changes interpreted as degeneration of elastic fibers were described in the coronary, renal, pancreatic, uterine, cutaneous, and mesenteric arteries as well as the splenic

trabeculae, hepatic veins, and Brück's membrane of the eye. In the patient of Urbach and Wolfram,[75] a 49-year-old man, who died with a Korsakoff-type psychosis and who had widening of the aorta by x-ray, identical histologic changes were found in the brachial, cutaneous, and cerebral arteries and in Brück's membrane. They also described and illustrated histologic changes in the aorta, which are, in my opinion, probably merely those seen in the senile aorta, sometimes even at the age of 49 years.

Carlborg[9] recorded autopsy observations made by another physician without particular knowledge of, or attention to, this syndrome. Klein[40] also reported an autopsied case. Two other autopsied cases are described in full below.

In the original case, Balzer[1] described degenerative changes involving presumably the elastic fibers in the walls of the pulmonary alveoli. However, the patient was a 49-year-old stonemason, who died of extensive pulmonary tuberculosis. This may have been responsible for any changes observed in the lungs. Furthermore, in the autopsied cases of Prick[55] and Urbach,[75] no abnormality of pulmonary elastic tissue was found. One can only speculate about the possible basis of a miliary mottling of one lung field described in the x-ray of one patient[81] and observed in both lung fields of one of my patients (C.T., J.H.H. 582989). It is possible that repeated small interstitial hemorrhages with resultant hemosiderosis are responsible. Calcification in small vessels is another possible explanation. In this same patient, there are no evidences of pulmonary hypertension, and studies of pulmonary function show no definite abnormality. In patients studied by Van Embden Andres,[76] no abnormality of residual air volume, maximum breathing capacity, and vital capacity was discovered.

In the thyroid arteries removed during thyroidectomy there were described[38] abnormalities of the type seen in small coronary arteries in the first autopsied case below. Scheie and Freeman[58] biopsied the ulnar artery in one case and described "elastic tissue degeneration" with compensatory muscular hypertrophy. Without illustration, Kaplan and Hartman[37] described degeneration of elastic elements, especially internal elastic lamella, in the vessels of the stomach removed in a 23-year-old white woman because of gastrointestinal bleeding. Beadlike microaneurysms were also present.

Many of the patients have advanced and premature arterial changes indistinguishable from ordinary atherosclerosis and arteriosclerosis. It is not legitimate to argue that these are not integral components of PXE. PXE sets the stage for the development of these changes, unusually early in life and in unusually severe degree.

If PXE is truly a dystrophy of collagen (viz. seq.), it seems a bit peculiar that the collagen matrix of bone does not participate in the basic abnormality of this syndrome.

THE BASIC DEFECT

Whether PXE is a dystrophy of elastic fibers or of collagen fibers has been much debated. Certainly the degenerate material which develops in the skin has certain tinctorial characteristics of elastic fibers. Findlay[18] has reported

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that the enzyme elastase removes this material from sections of skin from PXE patients. However, elastase is not entirely specific, e.g., it is said[30] to dissolve mucoproteins, behaving, therefore, fundamentally as a mucase. Furthermore, other studies[2] with elastase indicate some effects on normal collagen.

The evidence that PXE is an abiotrophy of collagenous rather than elastic fibers is as follows[32,76]: (1) Normally the skin contains relatively few elastic fibers. Elastin makes up only about 2 per cent of the dry weight of skin.[18] Collagen, on the other hand, constitutes about 72 per cent. The few elastic fibers present are concentrated immediately beneath the epidermis, and serve, according to one view,[18] a principal function of attaching the epidermis to the corium. (A defect in these fibers[68] may be responsible for the lesions of epidermolysis bullosa. These points are moot, however.[41,49]) The lesions of PXE are located in the deeper layers of the corium and are more extensive than can be accounted for on the basis of the normal amount of elastic fibers in the skin. The skin of the soles and palms is more liberally supplied with elastic fibers, but PXE lesions do not occur there ordinarily. (2) The arteries predominantly involved are the so-called muscular arteries, the media of which contains collagenous fibers but little elastic tissue. (3) The tunica elastica interna of these vessels (except in one report[37]) remains intact. (4) Except for their orceinophilia, most of the abnormal fibers resemble collagen fibers more than elastic fibers, because of their width. (5) Electron microscopic studies[74] reveal that the dystrophic fibers, although abnormal in other respects, have the characteristic 640 Å. periodicity of collagen. It appears, then, that in PXE the collagen may undergo dystrophic chemical or physicochemical changes with resulting acquisition of the tinctorial characteristics of elastic fibers. (6) There has been no acceptable clinical or pathologic evidence of abnormality arising from a defect of elastic tissue in the lungs.

Gillman and his co-workers[24] make important observations on what appears to be a rather widely occurring phenomenon. This they term "elastotic degeneration of collagen fibers." Irradiation, trauma, and aging appear to be responsible. In addition to degeneration of existing collagen fibers, the authors admit the possibility that there may be a disturbance of formation of new collagen fibers with the result that a simulation of elastic fibers results. By means of a battery of many staining procedures the authors showed that there are distinct differences between "normal" elastic fibers of skin and arteries and "elastotically degenerated" collagen fibers at the same site. Although no studies of PXE were made, the important observations of the South African group are probably pertinent in connection with this hereditary syndrome: "elastotic degeneration" of collagen can occur on either an acquired or a hereditary basis. In both, fragmentation and calcification occur.

Potentially very important observations have been made by Weidman, Anderson, and Ayres,[78] Pautrier,[52] and Lever[44]: young asymptomatic individuals may show in the skin abundant, irregularly branching, thick, nonfragmented fibers with the tinctorial characteristics of elastic fibers. The implication has been that these are individuals who would subsequently develop typical PXE and/or are members of kinship containing other definite cases. However, to my

knowledge, this implication has not been established except possibly in one patient of Van Embden Andres,[76] who had central chorioretinitis of the type seen in PXE and by skin biopsy "hyperplasia of elastic fibers without elastorrhexis." If it is further confirmed that these individuals with what Weidman calls "juvenile elastoma" are indeed instances of predegeneration PXE, it would mean that a quite unique type of connective tissue fiber is produced in these individuals and undergoes degeneration with physiologic stresses. It would mean, furthermore, that the efforts to relate the basic defect to collagen or to elastica is pointless. I find it difficult to believe that these cases of Weidman and others are related to PXE, mainly because there should be identifiable in one and the same individual, areas of as yet nondegenerate "elastoma" and other areas of typical PXE.

The pathogenesis of the angioid streaks is unsettled.[13] The theory propounded by Kofler[42] in 1917 is that breaks in Brück's membrane explain this finding. After reviewing the matter, Cowper[13] recently concluded that the original view (that the primary difficulty is a degeneration and sclerosis of the choroidal arteries with secondary changes in the retina and in Brück's membrane) seems more consistent with the known facts.

Whatever the element of connective tissue basically affected, certain it is that the clinical behavior is that of an abiotrophy. The predominant involvement of areas of the skin exposed to maximum wear and tear such as flexion folds, belt line,[5] pressure points, etc., is striking.

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INCIDENCE AND INHERITANCE

PXE probably occurs quite generally without particular racial distribution. The two autopsied patients at this hospital were both Negroes. In addition to being described in natives of many European countries including Turkey,[48] it has been observed in Japanese.[50]

Some indication of the incidence of PXE is provided by the fact that 125 cases of associated skin and fundus changes and 68 cases of skin changes alone had been described previous to 1940.[67]

There can be no doubt of the hereditary nature of PXE. However, of the five syndromes under detailed discussion in this series, the genetics of PXE is probably the least firmly established. Part of the difficulty resides in the fact that manifestations appear only more or less late in life. Furthermore, the changes are often subtle (see Fig. 2). Finally, the ocular changes may be asymptomatic and require special examination for demonstration.

Touraine[71,72] found 46 families with more than one affected person—a total of 104 persons. Inheritance as an autosomal recessive is suggested but by no means proved by the occurrence of multiple cases in individual sibships and by the rarity of its occurrence in successive generations.[33,48,62] In 1941, Scholz[59] could find reports of 18 cases of angioid streaks in which one or more siblings were similarly affected; in four cases the parental union was consanguineous. In the case of the skin changes, consanguinity was noted in the two sisters reported by Throne and Goodman[69]; the parents were first cousins. Up to 1933, Cockayne[12] could find reports of 5 kinships which contained multiple cases and in which the

status of full sibships was given. In these families there were 13 affected and 12 normal persons. In 8 families containing more than one affected person, there were 4 males and 13 females affected. In general, a preponderance of females affected by this syndrome has been noted. (However, in my own group of 16 patients, 8 are female). Touraine[71-73] counted 52 women among 73 cases of the skin changes, among 92 cases of both eye and skin changes there were also 52 women. Thus, in a total group of 165 cases, 104 were women. Cockayne[12] concluded: "This condition will almost certainly prove to be recessive to the normal, and partially sex-limited to the female." The ratio of about 1:1 of affected to unaffected sibs rather than the 1:3 ratio expected of a recessive trait may be in part an artefact of ascertainment: many sibships which, as far as the genetic make-up of the parents was concerned, might have had an affected individual, did not because the sibship was too small for the one-in-four probability to express itself; on the other hand, only sibships which contained an affected member were recognizable and included in the tabulation.

Témine,[67] writing in 1940, pointed to reports in the literature of the occurrence of this disorder in a parent and offspring seven times and in three successive generations twice. Since 1940 there has been at least one report[51] of direct transmission. Multiple cases occurred in a single sibship twenty-four times. Parental consanguinity was noted in at least six reports and was specifically stated to be absent in seven. A brother, a sister, and their maternal aunt were reported by Jones, Alden, and Bishop[36] as affected.

The series of 20 patients studied personally by Van Embden Andres[76] is of interest. Of these cases 13 were male. Fourteen families were represented. More than one sib was affected in at least four of these families. There was no example of the disease in successive generations of one family. Consanguinity was present in the case of three of the fourteen pairs of parents.

In summary, it probably can be concluded that there is more than one genotype of what phenotypically is PXE; that the most commonly occurring type is inherited as an autosomal recessive with partial limitation to the female; that rarely the syndrome may demonstrate inheritance as an autosomal dominant; that no clinical differences (phenotypic distinctions) between these two genotypes of the syndrome are definable.

The observation that skin in "asymptomatic" young subjects may show hyperplastic, predegeneration changes (see above) has never been used in connection with pedigree studies.

MISCELLANEOUS CONSIDERATIONS

There is no definitive treatment for this disorder. Tocopherol (vitamin E) was said[63] to effect dramatic improvement in the skin and eyes of one patient. Good cosmetic effects have been reported by plastic surgeons,[11,54] who have removed the loose, excess skin around the neck, which may be distressingly unsightly, especially in women.

It seems conceivable that a fundoscopic picture indistinguishable from that of the angioid streaks seen with PXE may occur on other bases than this particular genetic one. For example, angioid streaks are encountered in association

with Paget's disease. However, PXE is the most common basis for the finding. Scholz[59] stated that, previous to 1941, 59 per cent of 139 cases of streaks had the skin condition. On the other hand, in a series collected from the literature, Goedbloed[25] found 57 cases with skin involvement among 67 with streaks, and Sanbacka-Holström[57] found 87 out of 100 cases. Although angioid streaks may occur with either PXE or Paget's disease, there is, to my knowledge, only one adequately described instance of the occurrence of changes in the skin, fundus, oculi, and bones of the same individual. Woodcock[82] described a 54-year-old white man with bilateral angioid streaks, skin changes of PXE in the axillae, and Paget's disease as manifested by cephalic enlargement, bowing of the legs, spontaneous fractures, renal calculi, and characteristic radiologic changes. Sanbacka-Holström[57] refers in passing to such a patient, and there are loose references to the coincidence of the three manifestations in textbooks and reviews. There is good reason (see Section VIII of this series) to think that there is no fundamental relationship between PXE and Paget's disease. One reason is that Paget's disease usually behaves like an autosomal dominant. Furthermore, it is more frequent in men.

Reduced pulse wave velocity in the vessels of the extremities was found in the great majority of cases of PXE,[9,76] and the pulse wave was of reduced amplitude and plateau configuration.

Clinically, the skin changes in senile elastosis are somewhat similar to those of PXE. The conclusion of Percival, Hannay, and Duthie[53] was that this too is a dystrophy of collagen rather than of elastic fibers. Histologically, however, senile elastosis is characterized by a diffuse involvement in the superficial parts of the corium, less marked basophilia to hematoxylin and eosin stain, the absence of involvement in more or less circumscribed areas of any one section, and, finally, the usual lack of fragmentation of the dystrophic fibers into granular material. I know of no evidence of an hereditary background in senile elastosis. It may represent a breakdown of basically normal collagen occurring as a result of acquired factors but occurring along lines somewhat similar to that by which genetically weak collagen breaks down under much less stringent acquired stresses.

CASE REPORTS

Case 1.—R.K. (J.H.H. 156572), a Negro man, born in 1891, died in 1954 from accidental mercury poisoning.

The family history was largely unknown. He had no children.

About 1932 the patient was found to have a positive serologic test for syphilis, and treatment with arsenicals, mercury, and bismuth was given at another hospital where he had gone because of failing vision. He was first seen at this hospital in 1938 because of continuing dimming of vision. He had worn spectacles for about six years with no apparent staying of the visual failure in spite of several changes. Bilaterally the entire macular area was the site of atrophy and scarring. The vessels were normal. Running out from each disc in all directions were wide, branching, brownish streaks. About the neck he was noted to have many linear 4 or 5 mm. yellowish papules about 1 mm. thick. These were arranged parallel to the clavicle and coalesced in many areas to form short streaks several centimeters in length. The diagnosis of PXE with angioid streaks was made and confirmed by skin biopsy (Skin Path. #9606). On general examination the patient was noted to have an arcus senilis bilaterally. The blood pressure was 170/90 mm. Hg. No pulse changes or circulatory abnormality in the legs or elsewhere were detected by history or examination.

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The patient was visited in his home several times late in 1953, but refused to come to the hospital for investigation of his connective tissue disorder. He was now almost completely blind. For many years he had been suffering from intermittent swelling and pain of the proximal interphalangeal joints. He had also had much pain in the tibial and calf areas as well as the knees. He had developed ulcerations of the pretibial area and made a practice of soaking these with bichloride of mercury solution. He took Dolcin, a proprietary analgesic, for his aches and pains. Several years previously he had been told that he had diabetes mellitus.

About 6 A.M. on Jan. 11, 1954, the patient went to take Dolcin tablets for relief of pains in both shins and, because of his faulty vision, took three tablets of bichloride of mercury instead. He first noted burning of his mouth and thereafter pain in the mid-epigastrium, accompanied by the vomiting first of a large amount of clear yellow fluid and later of bright red blood of unknown quantity. Severe persistent bloody diarrhea followed. He was seen by his family physician, who could record no blood pressure and sent him to the hospital, where he arrived about eight hours after the accidental ingestion of mercury.

The patient had been noted to be easily confused in recent years, and therefore the exact details of the history of the final days of life are not entirely certain.

Physical examination revealed the skin of the neck, axillae, inguinal areas, and anterior abdominal wall to be nodular and leathery. It was strikingly inelastic, but this may have been in part the result of dehydration. All interphalangeal joints showed fusiform enlargement, and nodules were located around the knuckles. The heart showed a loud blowing apical systolic murmur and rather numerous extrasystoles. Femoral pulses were present but none could be felt in the popliteal fossae or feet. There were two large depigmented scars with some unhealed and scabbed areas on both pretibial prominences.

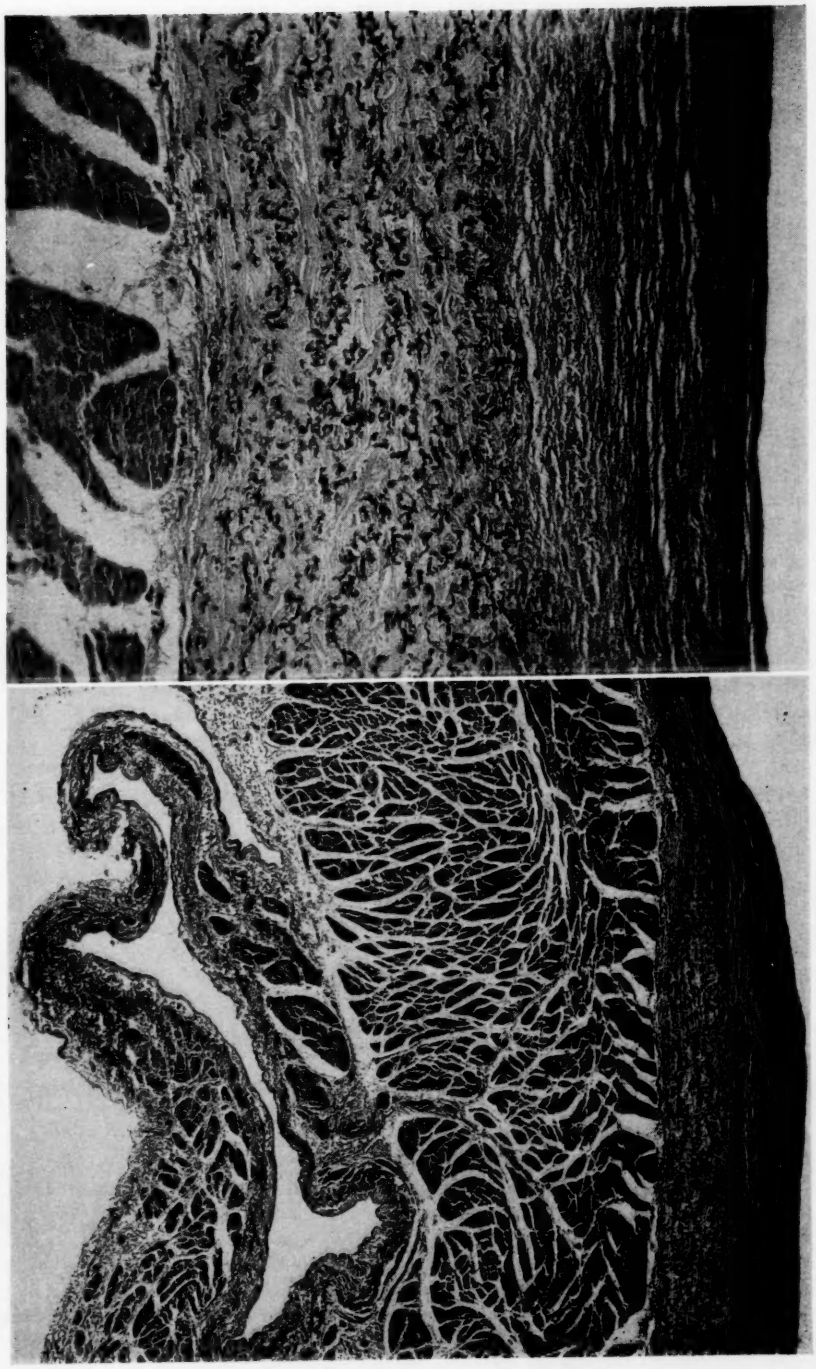
The patient was virtually anuric throughout his hospital stay, and died on the sixth hospital day. The diagnosis of mercury poisoning was corroborated by the finding of 6 mg. of Hg^{++} per 20 c.c. of stomach fluid taken at admission. Death occurred despite the use of BAL and supportive measures.

Autopsy (#24837) was performed ten hours after death by Dr. H. M. Hill. (In spite of the delay, fibroblasts grew out in tissue culture from explants of skin and of aortic adventitia.) The body weighed 50 kilograms and measured 168 cm. in length. The changes in the skin and joints and the juxtarticular nodules were observed as during the clinical examination.

The heart weighed 325 grams and did not appear to be enlarged. A most impressive finding was thickening of the endocardium of the right atrium. This was somewhat yellowish in coloration, and over the trabecular ridges there were peculiar nodular thickenings. The posterior leaflet of the tricuspid valve had a smooth, thickened, firm, rolled edge without excrescenses. The aortic leaflet of the mitral valve was similarly thickened at the edge and there was marked calcific change at its attachment. The coronary ostia were normal, but everywhere the coronary arteries were exceedingly sclerotic and calcified, with reduction of their caliber to little more than a pin point.

The aorta was of normal caliber with only minimal atherosclerosis in the abdominal portion and normal elasticity by gross test. There were marked calcification and narrowing of the femoral, popliteal, and posterior tibial arteries. These changes were particularly striking at areas of bending, such as in the popliteal fossae. The posterior tibial arteries were exceedingly beaded. The vessels at the base of the brain were sclerotic. Grossly and histologically there were characteristic changes of mercury poisoning in the kidney and gastrointestinal tract.

Histologically, the corium, the sclera, and the subendocardial area of the right atrium showed the same changes which have been frequently described previously in the skin of patients with PXE. Faintly basophilic (by hematoxylin and eosin stain), fragmented material was concentrated most heavily in the mid-dermis. This material was present in great abundance in the clinically involved areas and present sparsely elsewhere. This material had the tinctorial characteristics of elastic tissue. The popliteal and coronary arteries showed marked medial and intimal sclerosis and calcification. As demonstrated in Fig. 3,*C*, branches of the coronary artery supplying the right atrium showed changes in the media comparable to those in the atrial endocardium and corium.



B.

A.

Fig. 3, *A* and *B*. *(For legend see opposite page.)*

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C. *D.*

Fig. 3.—Autopsy, Case 1. *A*, Wall of right atrium. (×25. Hematoxylin and eosin stain.) On the endocardial surface (below) one of the opaque, elevated placques is seen in section. On the epicardial surface a branch of a coronary artery is seen. *B*, Enlarged view of one part of the field in *A*. (×100. Hematoxylin and eosin stain.) Striking similarity to the changes in the skin is evident (see Fig. 1, *E*). *C*, Enlarged view of another part of the field in *A* to show the changes in the wall of the artery, which again are identical to those in the skin and endocardium. (×100. Hematoxylin and eosin stain.) *D*, Elastic fiber stain of aorta. (×50.) The intima (on right) is thickened but the media shows no striking disorganization.

Comment.—Of particular interest are the histologic changes in the endocardium of the right atrium and in the sclera. Neither site normally demonstrates more than a very sparse distribution of elastic fibers. The deforming arthropathy is likewise of special note. The manifestation has not been commented on previously in cases of PXE. Unfortunately, no histologic studies of either joint structures or juxtarticular nodules were performed.

CASE 2.—C.J. (J.H.H. 292168), a Negro woman, born in 1896, was seen here on several occasions in 1943 and died at this hospital on Jan. 1, 1944.

Her mother died of a stroke at the age of 48 years. The patient had four brothers: two died in childhood, one shortly after discharge from Army in World War I, and one was living and well. The patient had sixteen children, of whom seven were living in 1943. No other instance of PXE was known to have occurred in the family. However, the family has not been traced and studied with this point specifically in mind.

The patient's eyesight had always been poor but had become worse in the last year of life. She noted tarry stools on several occasions and complained at times of epigastric burning. Early in 1943 she developed anginal symptoms for the first time.

Examinations revealed a blood pressure of 190/110 mm. Hg. There was evidence of marked weight loss (about 50 pounds in one year). The skin was everywhere very loose, due in part to PXE. The neck veins were full and dilated but not the arm veins. The heart was enlarged to the left anterior axillary line. The patient was so debilitated that carcinoma was suspected. Directly above the umbilicus there was a placque of smooth skin containing small, hard, elevated nodular areas. Histologically (Skin Path. #5157) there were changes typical of PXE. The fundi showed no angioid streaking, but fairly marked hypertensive and sclerotic changes in the arteries, many hemorrhages, and in the macula area many yellow shiny placques.

Total serum protein was 8.3 Gm. per cent, of which 5.5 Gm. per cent was globulin. Biopsy of the skin from about the umbilicus revealed typical changes of PXE with calcification. Hemoglobin was 10.5 Gm. per cent. Electrocardiogram revealed left axis deviation, left ventricular strain pattern, and prolonged AV conduction. On chest x-ray, calcification in superficial vessels in the left axilla was demonstrated. The aorta was dilated and tortuous. On barium swallow the esophagus was relaxed and tortuous. Gastric analysis revealed normal acidity.

After four months away from the hospital, during which time she had become steadily weaker, the patient was brought back to the hospital with massive leg edema and ascites and with Cheyne-Stokes breathing. She died two hours later.

Autopsy (#18717) revealed marked generalized arteriosclerosis, arteriosclerotic and arteriolosclerotic nephritis with Kimmelstiel-Wilson type lesions of glomeruli, coronary sclerosis with myocardial scarring. In addition, there were tuberculous peritonitis and caseous obstruction of the thoracic duct with chylous ascites. The aorta was atheromatous with a few ulcerations.

Comment.—Hyperglobulinemia was probably due to tuberculosis. It was of interest that Kimmelstiel-Wilson lesions occurred in this nondiabetic individual. In general, premature and severe arteriosclerosis dominated the clinical picture and the findings at autopsy. What relation there may have been between the skin changes and the vascular disease is unclear. In general, however, this patient demonstrates the early and rapidly progressive dissolution of the vascular system characteristic of patients with PXE.

SUMMARY AND CONCLUSIONS

The clinical manifestations of pseudoxanthoma elasticum include (1) characteristic skin changes, occurring especially in areas of wear and tear; (2) angioid streaks of the fundus oculi; and (3) either hemorrhage, symptoms of ischemia, or

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hypertension, resulting from arterial degeneration. Gastrointestinal hemorrhage is the complication of most importance to the internist.

Evidence on the nature of the basic defect is reviewed, and it is concluded that collagen is most suspect as being primarily involved in this abnormality which behaves as an abiotrophy.

Descriptions of two autopsied cases are added to the meager information available on the state of tissues other than the skin and eye. In one case, changes completely unique to PXE were demonstrated in the endocardium of the right atrium, and in small branches of the coronary arteries. Both cases had advanced atherosclerosis and arteriosclerosis.

This disorder is most often inherited as an autosomal recessive. Partial sex limitation appears to result in its occurrence in females more frequently than in men. Occasionally inheritance as an autosomal dominant seems to be the case.

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A TEMPOROMANDIBULAR JOINT PAIN-DYSFUNCTION SYNDROME

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(Received for publication Oct. 15, 1955.)

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FACIAL pain which does not respond readily to simple treatment is often alarming to the patient and perplexing to the practitioner. When pain is believed to arise in the temporomandibular joint, treatment is often radical. Administering cortisone, infiltrating the joint with a sclerosing agent, excising the meniscus, and altering the occlusion of the teeth through radical dental treatment, are some of the methods used. Spasm of the masticatory muscles has been found to be a common cause of facial pain. In such cases, pain is accompanied by dysfunction of the mandibular muscles, the symptoms constituting a temporomandibular joint pain-dysfunction syndrome. This syndrome responds to conservative treatment. Since heroic measures are rarely successful, the presentation of some simple effective office procedures seems timely.

THE TEMPOROMANDIBULAR JOINT

The temporomandibular joint is unique in form and unusual in function. The physiology of this joint, a subject of much controversy, is as yet not clearly understood. Agreement centers mainly about its structure. This is understandable since the anatomy of the temporomandibular joint has been known for centuries. Vesalius[1] first observed the articular disc during the sixteenth century, and John Hunter[2] in 1771 described this articulation between the mandible and the cranium so completely that there has remained little to add. The temporomandibular joint is a highly specialized joint. It is divided into two compartments by an articular disc or meniscus interposed between the head of the condyle of the mandible and the mandibular fossa of the temporal bone creating a double joint with two pairs of articulating surfaces. Another distinguishing characteristic is that the temporomandibular joints, attached as they are to the end of the U-shaped mandible, constitute the only system of yoked joints in the human body. Neither joint functions without the other.

The mandibular joints are loose, hanging joints. Through their ability to turn in practically all directions as they glide, they permit the mandible an extremely wide range of movement. This versatility of movement has pre-

Read before the Annual Meeting of the New York Rheumatism Association, April 20, 1954, under the title, "The Clinical Physiology and Pathology of the Temporomandibular Joint."

occupied dentists for over fifty years. The temporomandibular joints have been studied for the purpose of reproducing jaw relationships and mandibular movements mechanically on an instrument called an articulator. Many different articulators have made their appearance. No single one has been generally accepted, and the dependability of any articulator has been seriously questioned.[3]

This practical, mechanical approach to temporomandibular joint function continues mainly because dentists are daily confronted with difficult clinical problems in the making of prostheses. First used only in artificial dentures, this approach was in time applied to the occlusion of the natural teeth. Costen, an otolaryngologist, has stressed the relationship between the occlusion of the teeth and symptoms believed to arise in the temporomandibular joint.

COSTEN'S SYNDROME

In 1934, Costen[4] described a symptom-complex which now bears his name. The group of symptoms which he[5] described as occurring uniformly in disturbed function of the temporomandibular joint were: (a) ear symptoms such as loss of hearing, stopping of the ears, tinnitus, pain, and dizziness with nystagmus; (b) pain in the form of headache about the vertex, occiput, and behind the ears, and a burning sensation in throat, tongue, and side of the nose; (c) miscellaneous symptoms such as dryness of the mouth, herpes of the external ear canal and buccal mucosa. In 1938, Costen[6] added trismus to his syndrome. He believed all these symptoms to be caused by altered temporomandibular joint function due to overclosure of the jaws resulting from loss of posterior teeth. He and others reported improvement following "raising" of the bite for the purpose of establishing "normal" relationship of the condylar heads within the glenoid fossae. Practiced widely at first, this form of treatment, as well as the existence of the syndrome itself, has been questioned.[7,8]

INVESTIGATIONS OF THE TEMPOROMANDIBULAR JOINT CLINIC

Two hundred and fifty-six patients, mainly women, suffering from symptoms associated with the temporomandibular joint, were examined at the Temporomandibular Joint Clinic, a research clinic of the School of Dental and Oral Surgery, at the Columbia-Presbyterian Medical Center. The symptom-complex described by Costen was not found. Pain and dysfunction in the form of limitation of mandibular movement were the symptoms most frequently encountered in this group of patients, reported in 1954.[9,10]

The pain described by these patients differed from the sudden, paroxysmal and irregular pain of the neuralgias. It was usually described as a unilateral, constant, dull earache or jawache initiated or aggravated by jaw movements and sometimes spreading to the head, neck, and shoulder. Diagnostic surveys, with the cooperation of many departments of the Medical Center, disclosed an extremely low incidence of temporomandibular joint disease (less than 3 per cent). The investigations of Ragan[11] also pointed to the resistance of this joint to disease. In rheumatoid arthritis, he found that the incidence of temporomandibular joint involvement was 4.5 per cent, compared with 92 per cent in the joints of the fingers.

Muscle tenderness was often found among patients suffering from temporomandibular joint pain and dysfunction. This tenderness was located in various antigravity muscles of the jaws, neck, and shoulder (masseter, internal pterygoid, temporalis, posterior cervical, and trapezius) as well as the sternomastoid. The nature of the symptoms, dull ache with limitation of movement, suggested a pain-spasm cycle of the type described by Travell[12] and Kraus.[13] The effectiveness of ethyl chloride spray[9] and of intramuscular infiltration with a local anesthetic[10] followed by the exercising of the masticatory muscles supported this conclusion.

THE TEMPOROMANDIBULAR JOINT PAIN-DYSFUNCTION SYNDROME

Continuing studies[14] are confirming the 1954 findings.[9,10] In an amplified recent four-year study, 377 (77.8 per cent) of 491 patients examined (398 female and 93 male) presented symptoms in the form of a complex—a temporomandibular joint pain-dysfunction syndrome.[15]

This syndrome often was precipitated by sudden or continuous stretch of the masticatory muscles, as in a yawn, wide bite, dental treatment, or by proprioceptive changes caused by sudden or extensive alterations in the dental occlusion through treatment. Predisposition, psychologic as well as physiologic, seems to be more important than the particular form of the precipitating factor itself. Tensional factors were evident among many patients, some of whom had psychiatric interviews.[16] Emotional tension was often manifested by a history of oral habits such as clenching or gnashing the teeth. Dental malocclusion in the group studied was too universal and too varied to permit detailed evaluation. It is believed, however, that malocclusion in most cases was but a contributing factor.

THERAPY

Therapy consists, in general, of the use of local anesthetics to relieve pain, followed by therapeutic exercises to restore function. The exercises used were devised by applying to the mandibular muscles the general principles and practices of therapeutic exercises.[13] The type of exercise utilized depended upon the type of dysfunction. It has been found, for example, that a functional incoordination of mandibular muscles with symptoms such as clicking and recurrent subluxation or dislocation of the temporomandibular joint often precedes the pain limitation phase. It has also been observed that incoordination symptoms often reappear after pain and muscle spasm are relieved. It is these last symptoms, however, in the form of limited, painful mandibular movement, which were found most frequently.

Limitation.—The exercises used were of necessity varied to meet the particular clinical problem at hand. The pain-limitation syndrome varies from those cases in which pain is predominant and limitation minimal, to those in which limitation is marked and pain occurs only when forcible opening is attempted. When pain is acute, as in a painful muscle spasm of short duration, exercise is not attempted until, through the use of local anesthetics, relatively painless movement is possible. The degree of opening should not be such as to cause a

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great deal of pain. Ethyl chloride spray or procaine infiltration of muscles should be used to enable the patient to function painlessly. While patient is lying on his back he is asked to move his mandible in gentle rhythmical alternating movements gradually increasing the range. Acute painful spasm of the masticatory muscles often responds to a single treatment.

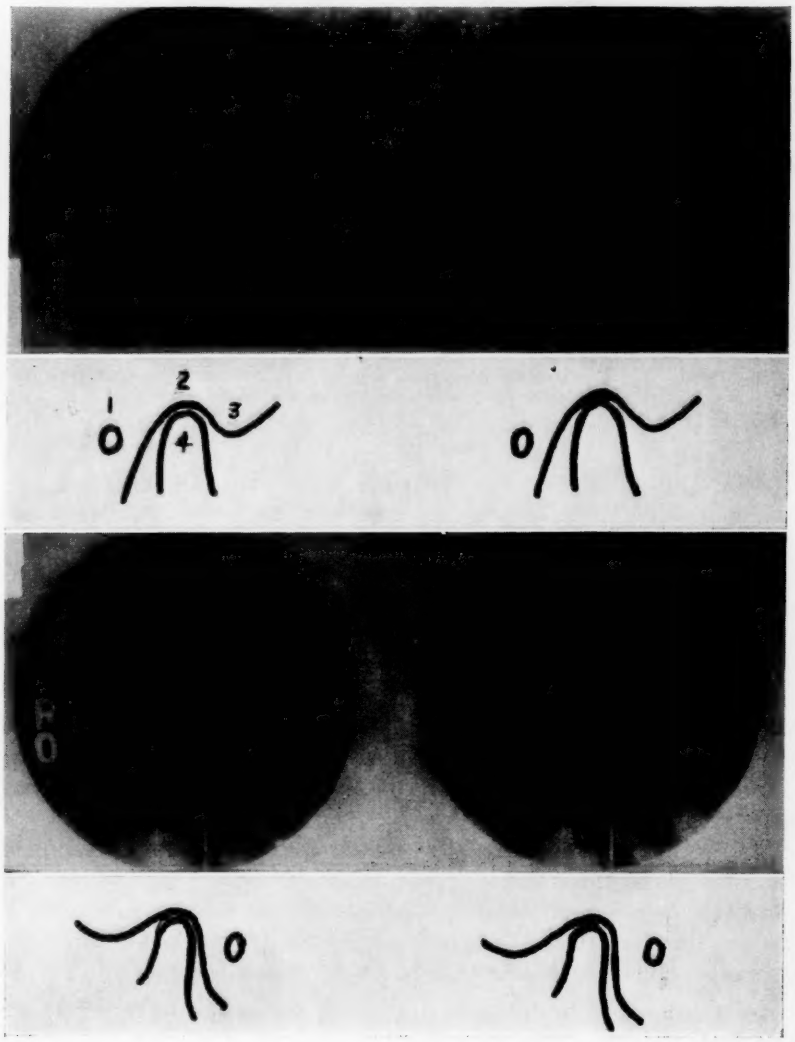
Fig. 1.—A method of relaxing the masticatory muscles. By having the patient open against resistance, the muscles which elevate the mandible are relaxed reflexly.

Recovery is less rapid when the symptoms are of longer duration. In such cases, by resisting the opening movement of the mandible the masticatory muscles are relaxed reflexly. With the patient lying on his back on the examining table, his head is held firmly with one hand, his mandible with the other (Fig. 1). The patient is asked to open and close his jaw in rhythmical hinge-like movements against the resistance of gentle hand pressure. After approximately ten movements, the patient is asked to open as wide as he can three times, still against hand resistance. In this way, through the combined action of the suprahyoid and infrahyoid muscles, the masticatory muscles are stretched. The exercise is repeated at least three times. The intermaxillary distance after treatment compared with that found before will indicate the effectiveness of treatment.

Little or no response, especially with a long history of limitation, suggests the possibility of contracture. It is presumed that in this condition fibrotic changes have occurred in the muscles. As a rule, the shorter the duration of the symptoms, the more rapid is the response to treatment. With cooperative patients, self-treatment at home has been found to be effective.

Incoordination.—The treatment of the symptoms of incoordination of the mandibular muscles—clicking, subluxation, or dislocation—is more complex and less dependable. Fortunately, these symptoms are met less frequently than limitation, and aside from actual dislocation do not incapacitate the patient.

The symptoms of limitation are relieved as soon as the particular masticatory muscles which are in spasm give up their tension and regain their physiologic elasticity. Incoordination, when it is functional (as it is in this syndrome), may be caused by either poor muscle elasticity, poor muscle power, or both. Hence, in addition to relief of muscle spasm, it is also necessary to build the power of particular muscles through the use of suitable exercises. For example, clicking is often relieved with exercises designed to improve the power of the masticatory muscles which retrude the mandible, the deep fibers of the masseter, and the posterior fibers of the temporal.



*A*₁

Fig. 2.—Radiographs showing the appearance of anterior condylar movement in a patient in whom this movement was absent during a temporomandibular joint pain-limitation syndrome. *1*, External auditory meatus; *2*, mandibular fossa; *3*, articular eminence; *4*, head of the mandibular condyle. *A*, Radiograph before treatment (March 26, 1954) discloses the absence of anterior (translatory) movement of the condylar heads (*4*) during opening. Views taken in the open positions (*RO* and *LO*) compared with the closed positions (*RC* and *LC*) show practically no change.

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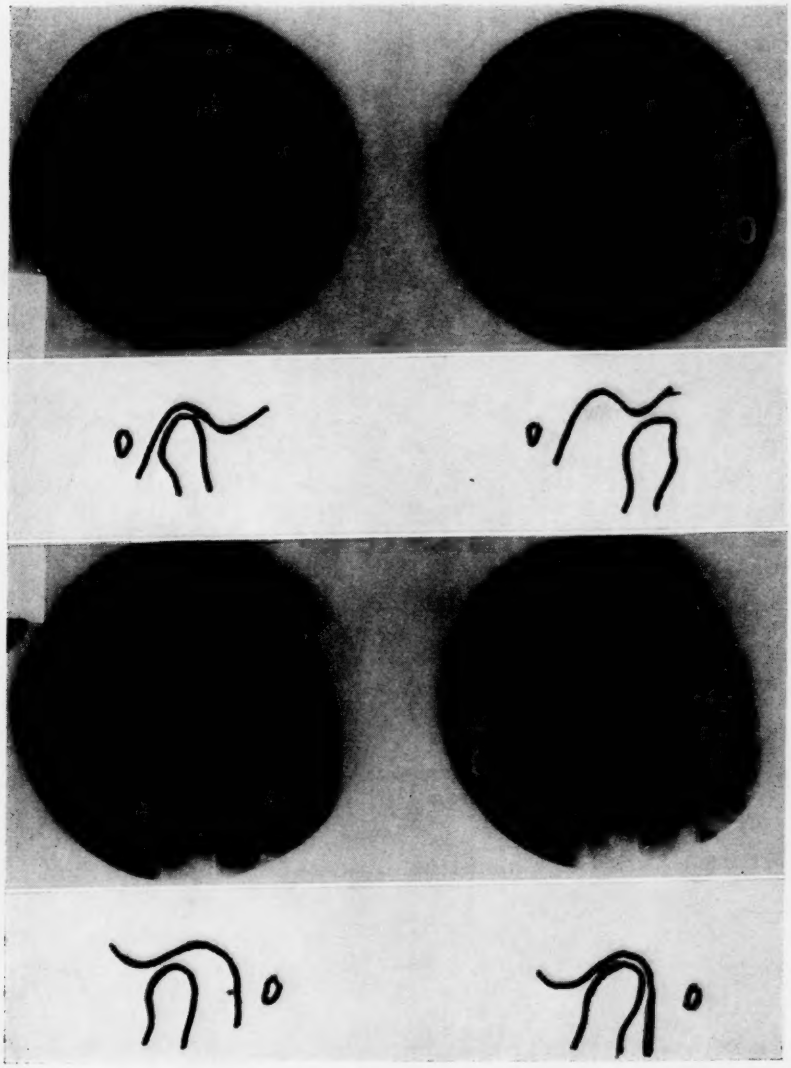
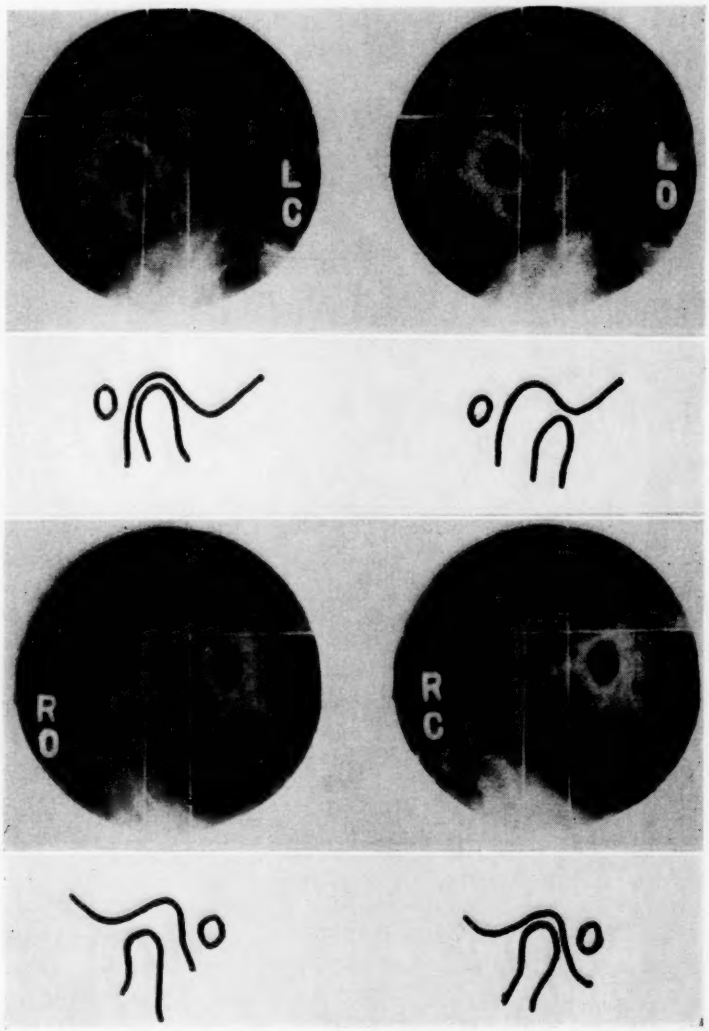
Altering the Occlusion of the Teeth.—Because dental treatment is unavoidably traumatic, psychologically if not physiologically, alteration of the occlusion, when considered necessary, was delayed until improvement was evident. Treatment of this kind was approached cautiously since no matter how accomplished, it does alter proprioception. Moreover, dental treatment results in changes which are usually irreversible. Patients suffering from temporomandibular



B.

Fig. 2 (Cont'd).—*B*, Radiograph after treatment (April 7, 1954) discloses that on the right side in the open position (*RO*) the condylar head (*4*) moves anteriorly out of the mandibular fossa (*2*) approaching the crest of the articular eminence (*3*). On the left side (*LO*) the condylar head (*4*) moves beyond the crest of the articular eminence (*3*).

joint syndromes do not adapt easily to such changes. The attitudes and experiences of many patients contraindicated dental treatment. Some patients attributed their difficulties to such treatment. In the experience of others, alteration of occlusion had failed to relieve or had even aggravated the symptoms. Modification of occlusion is a valuable adjunct in the treatment of temporomandibular joint syndromes. It must, however, be used judiciously and cannot be relied upon completely.



A.

Fig. 3.—Radiographs showing increase in the range of condylar movement in a patient in whom it was limited during a temporomandibular joint pain-limitation syndrome.

A, In radiograph before treatment (Oct. 30, 1954) the condylar heads (*4*) in the open positions (*RO* and *LO*) approached the crests of the articular eminences (*3*).

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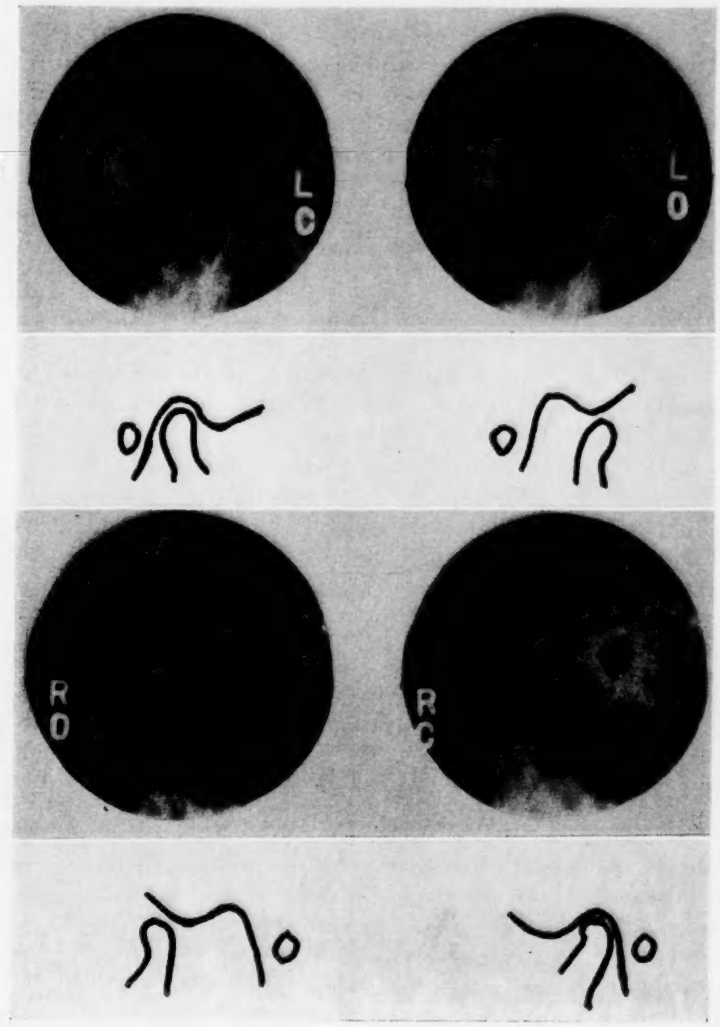
Other Types of Treatment.—The temporomandibular joints have been injected with sclerosing agents,[17] the meniscus has been excised,[18] the intra-articular use of hydrocortisone has been suggested as an adjunct to occlusal therapy[19] and the use of hyaluronidase has been reported.[20]

RADIOGRAPHY

X-ray examinations are helpful in both diagnosis and treatment. In addition to their value in revealing condylar fractures, neoplasms, and calcific changes due to collagenous disease, the radiograph can show the effects of muscle spasm on condylar movements.



B.

Fig. 3 (Cont'd).—*B*, After treatment (Jan. 12, 1955) the left condylar head (*4*) moved in the open position (*LO*) beyond the crest of the articular eminence (*3*). The right condylar head moved entirely out of the mandibular fossa (*2*) to the anterior slope of the articular eminence (*3*).

Through radiography, it is possible to see, in the limitation syndrome, the absence of anterior translatory movement of the head of the condyle as the mandible opens (Fig. 2*A*). As muscle spasm is relieved, the range of condylar movement increases (Fig. 2*B*). In some cases, though anterior movement of the condylar heads is present (Fig. 3*A*), their range is limited according to clinical findings. With treatment, the range of condylar movement increased (Fig. 3*B*).

While the radiograph is a valuable adjunct in diagnosis, a danger exists in the temptation to establish a geometrical norm. In Fig. 3*A*, during the opening movement, the heads of the condyles reach almost to the crest of the articular eminence, a position which has been described as normal.[21] Yet the patient complained of painful, limited mandibular movement. With the relief of muscle spasm the range of condylar movement increased (Fig. 3*B*). The right condylar head moved beyond the crest of the articular eminence toward its anterior slope—a position which has been described as dislocation.[22] Movement of the condylar heads well beyond the crests of the articular eminences has been found among many completely asymptomatic individuals with normal mandibular function. If such range of movement is to be considered dislocation, then the temporomandibular joint is a physiologically "dislocating" joint. Subluxation and dislocation are usually clinical manifestations of a functional incoordination of mandibular muscles, and consequently a diagnosis cannot be made from a radiograph.

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DIFFERENTIAL DIAGNOSIS

Diagnosis of a temporomandibular joint pain-dysfunction syndrome, either limitation or incoordination, is made as a result of a complete history and examination. Though the incidence of organic disturbances is low, such disorders must be ruled out. Signs and symptoms similar to those found in the syndromes may be due to organic disturbances of the temporomandibular joint itself, as in condylar fractures, neoplasms, and collagenous disease. Such signs and symptoms may also arise from diseases not involving the joint. Examples are disorders of the parotid gland, ear, and paranasal sinuses as well as dental and oral disease. It is also necessary to keep in mind the possibility of neurologic disorders such as the neuralgias and the diseases of the locomotor system.

COMMENT

Until a diagnostic impression of temporomandibular joint pain-dysfunction syndrome is reached, it is important to observe Osler's admonition regarding the need for "imperturbability" on the part of the physician.[23] Patients suffering from this facial pain syndrome, possibly because of the particular temperaments which predispose them, are apt to seize eagerly upon words spoken rashly by the dentist or physician. The danger of iatrogenic disease is great, and the means of preventing iatrogenicity suggested in a recent editorial[24] apply to the management of this syndrome. The phrase "tensional charleyhorse of the jaw" was found to be helpful, particularly in those cases where it was possible to relate the onset of symptoms to psychologically traumatic events brought out in the history.

In therapy, one must guard against the "urge for spectacular action."[25] Efforts should be directed mainly toward the alleviation of the pain, relief of muscle spasm, and the improvement of the coordination of the mandibular muscles by means of gentle, judicious treatment. The management of the emotional tension which is often at the root of the syndrome, except for those patients in whom anxiety is but transitory, presents greater difficulties. Most of the patients seen were not receptive to psychiatric treatment, and when lessening of tension was accomplished, it was achieved by means of patient explanation and sympathetic reassurance.

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HYPERGLYCEMIA AND GLYCOSURIA AFTER INGESTION OF GLUCOSE BY AMBULATORY PATIENTS OVER 40 YEARS OF AGE

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(Received for publication Sept. 28, 1955.)

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INTRODUCTION

THERE is little documented evidence on the course of diabetes mellitus from a stage in which the impairment of carbohydrate metabolism is minimal to that of constant hyperglycemia and glycosuria. The transition, however, has been directly observed and reported upon in a few instances.[1] Indirect support for the existence of such a transition also derives from the metabolic circumstances surrounding the birth of large infants to women destined later to develop frank diabetes mellitus.[2,3]

If a subject can be identified as manifesting a stage of early, mild impairment of carbohydrate metabolism, effective treatment can be instituted before manifestations become striking. Reduction of excess weight,[4] observation of blood and urine sugar at regular intervals, and, when necessary, treatment with diet and insulin are measures to be considered. While evidence is not at hand to prove the point, it seems reasonable to suppose that such a prophylactic and therapeutic program might spare a patient, demonstrated initially to have a mild impairment of carbohydrate metabolism, some of the complications associated with diabetes mellitus, such as certain infections and cardiovascular disease.

One of us, in association with Sauvé,[5] has previously reported experience with a technique for detecting minimal impairment of glucose tolerance in subjects in whom the fasting blood sugar level is normal and whose fasting urine contains no sugar; glucose was fed and the urine subsequently tested with Benedict's solution. Against the advantage inherent in the simplicity of the procedure it was found necessary to weigh the presumable disadvantage that the

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The data presented in this report appear in abstract form in the Proceedings of the Twenty-eighth Annual Meeting of the Central Society for Clinical Research, J. Lab. & Clin. Med. **46**:819, 1955.

*Dr. Marcus held a Fellowship in the Private Outpatient Service during the conduct of this investigation. His present address is: 5810 Cote St. Luc, Montreal, Canada.

feeding of glucose to some subjects is associated with the appearance of reducing substances in the urine which cannot be correlated with abnormal elevation of the blood sugar measured two hours after the ingestion of glucose. Thirty to forty per cent of subjects aged more than 40 years manifesting reducing substances in the urine during the test fell into this group,[5] which for statistical purposes was arbitrarily termed "false positive."

More recently we have performed this same test on 523 additional subjects who were undergoing diagnostic studies in the Private Outpatient Service of the Johns Hopkins Hospital and who were not previously known to have diabetes mellitus. With rare exceptions the subjects were aged 40 years or more. Two and one-half hours after the ingestion of 75 grams of glucose, Benedict's test was performed on a single specimen of urine and the amount of reducing substance recorded as "none, trace, 1+ to 4+" as the content varied from none to large amounts. On a subsequent day, 73 of the 99 subjects who excreted amounts larger than a trace were examined with a standard 100 gram, oral glucose tolerance test. The results are presented in Table I. In 37 (51 per cent) of the 73 subjects the venous blood sugar level, determined by the Folin-Wu technique, was below 120 mg. per cent two hours after the ingestion of the glucose; therefore, the initial urinary screening tests were classified "false positive." Thus our more recent experience substantiates our earlier conclusion, recognized by other workers,[6,7] that the interpretation of postprandial diabetic screening techniques employing only urinalysis is difficult and that such tests may advantageously be supplemented or replaced by observations of the blood sugar. It must be added that screening procedures employing a glucose meal and subsequent urinalysis or blood analysis have only recently been used by us; hence at present we lack information on the subsequent course of subjects demonstrated to have possible minimal impairment of carbohydrate metabolism by either analytical procedure.

TABLE I. REDUCING SUBSTANCE IN URINE AFTER INGESTION OF 75 GRAMS OF GLUCOSE BY 523 SUBJECTS

CONCENTRATION URINARY REDUCING SUBSTANCE	TOTAL SUBJECTS IN GROUP	NUMBER SUBJECTS WITH SPECIFIED TWO-HOUR BLOOD SUGAR LEVEL ON SUBSEQUENT TOLERANCE TEST		
		BELOW 120 MG. %	ABOVE 119 MG. %	NOT DONE
Negative	372			372
Trace	52			52
More than Trace	99	37	36	26

We have sought a simple method of screening patients for impaired carbohydrate metabolism which supplements urinalysis with a determination of the blood sugar. Our experience with the routine use of an abbreviated oral glucose tolerance test involving the measurement of the blood sugar of patients aged 40 years and over is described below.

OUTLINE OF TECHNICAL PROCEDURES

Chronology of Study.—The tolerance test was administered usually on the second to fourth day of the diagnostic study, one to two days after the initial measurements of the fasting blood and urine sugar. Frequently, however, all sugar studies were performed on the same day.

Subjects.—The 180 subjects of the present study comprised a group of ambulatory adult patients from upper economic levels who had requested diagnostic surveys for a variety of complaints in the Private Outpatient Service of the Johns Hopkins Hospital during the period March, 1954, through June, 1955. Many months previously, seven of the group had been screened for possible diabetes by a procedure involving feeding of glucose,[5] with negative results. The group included 10 Negroes. There were 83 males and 97 females. All were 40 years of age or older. No subject had been previously recognized as suffering from diabetes; none manifested striking symptoms of the disease. All underwent complete examination by one of the authors (P.H.F.) or by an associate (Dr. B. Robert Birely). The subjects included practically every patient in this specified category who was assigned to these two physicians during their routine duties in the clinic; the exclusion of any subject from evaluation by the tolerance test was governed by administrative rather than medical factors. All subjects were ambulatory. Some had no pressing complaints; the others suffered from the chronic illnesses encountered in any group of patients seeking the advice of an internist. Lewis[8] has reviewed the illnesses of a comparable group of patients examined in the same clinic. The records of all subjects have been reviewed for evidence of certain factors known to be associated with impairment of carbohydrate metabolism, and, as a result, a few patients were dropped from the series. Thus, none of the group we report upon presented a history of marked restriction of caloric intake in recent weeks, or evidence of rheumatoid arthritis, or of liver, thyroid, adrenal, or pituitary disease. No special laboratory procedures were routinely performed to exclude these last four conditions. None of the subjects we report upon was known to have been treated with adrenal or pituitary hormones during the period immediately preceding their examination.

The fasting blood sugar was measured in all of the 180 subjects; in no instance did it exceed 119 mg. per cent. Benedict's test for reducing substance was performed on the urine of all patients at some time preceding the glucose tolerance test. In the great majority of instances the specimen was obtained after an overnight fast. In only two of the subjects were reducing substances found in the urine. In neither of these subjects was the subsequent glucose tolerance test characterized by a two-hour sugar level in excess of 119 mg. per cent.

Conduct of the Abbreviated Glucose Tolerance Test.—The test was administered during the morning to subjects who had fasted since their meal the previous evening. After each subject had emptied his bladder, he drank, during a period of five minutes or less, a solution of 100 grams of glucose dissolved in 400 ml. of water flavored with lemon juice. Two hours after the glucose was completely ingested, samples of blood and urine were obtained. The blood glucose was

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determined with the Folin-Wu copper reagent after tungstic acid precipitation, according to the procedure ultimately described by Folin.[9] Reducing substance in the urine was identified by Benedict's technique[10]; 0.4 ml. of urine was added to 5 ml. of Benedict's qualitative copper solution (National Formulary). The subjects ingested no food and usually sat quietly during the test; in occasional instances an electrocardiogram was recorded during the two-hour period. Rarely, patients complained of nausea or other abdominal distress after ingesting the solution of glucose. No effort was made to standardize the intake of food during the days preceding the examination.

RESULTS

Blood Sugar.—Two hours after the ingestion of 100 grams of glucose, the venous blood sugar of healthy subjects, determined by the Folin-Wu technique, falls to a level below the range from 120[11] to 140[12,13] mg. per cent. During the course of the 180 tests on our 180 separate subjects, the blood sugar level two hours after the ingestion of glucose was observed to be in excess of 119 mg. per cent in 56 instances, including 29 subjects in whom it was in excess of 139 mg. per cent (Table II). These two groups constituted, respectively, 31 and 16 per cent of the 180 subjects. Our findings are compatible with the observation of others, summarized and extended by Schneeberg and Finestone,[14] who employed the more refined intravenous glucose tolerance test and concluded that subjects in older age groups frequently manifest impaired metabolism of glucose.

TABLE II. DISTRIBUTION OF 180 SUBJECTS ACCORDING TO AGE AND LEVEL OF BLOOD SUGAR TWO HOURS AFTER THE INGESTION OF 100 GRAMS OF GLUCOSE

AGE GROUP (YEARS)	TOTAL SUBJECTS IN GROUP	DISTRIBUTION OF SUBJECTS, BY BLOOD SUGAR LEVEL				
		BELOW 120 MG. %	120 TO 139 MG. %	140 TO 159 MG. %	160 TO 179 MG. %	OVER 179 MG. %
40–49	77	56	13	6	2	0
50–59	62	44	6	6	4	2
60–69	33	21	7	2	2	1
Over 69	8	3	1	2	2	0
Totals	180	124	27	16	10	3

As indicated in Table III, overweight was a frequent and possibly etiologically important finding in our hyperglycemic subjects.[4] The standard employed was the median of the "desirable" weight range for subjects of medium frame, as specified by the Metropolitan Life Insurance Company height-weight tables, edition of 1951. Subjects exceeding the standard by 20 pounds or more were termed "overweight"; those falling below it by 10 pounds or more, "underweight." Nine of the 13 subjects in whom the blood sugar level at two hours exceeded 159 mg. per cent were overweight. The data in Table III yield a chi square test of

significance. We are led to believe that an association does exist between overweight and an elevation of the blood sugar level two hours after ingestion of glucose. The association is not a strong one and has little practical importance in screening, for, if only overweight persons were subjected to the screening test, an appreciable proportion of the persons who showed elevated two-hour levels would have been missed.

TABLE III. CORRELATION OF DEVIATION FROM DESIRABLE WEIGHT WITH TWO-HOUR BLOOD SUGAR LEVEL DURING TOLERANCE TEST ON 180 SUBJECTS

BLOOD SUGAR (MG. %)	SUBJECTS			
	TOTAL	UNDERWEIGHT	NORMAL	OVERWEIGHT
Below 120	124	10	69	45
120–139	27	2	13	12
140–159	16	2	4	10
160–179	10	1	1	8
Over 180	3	1	1	1

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The males in our series accounted for 36 of the instances in which the blood sugar at two hours exceeded 119 mg. per cent and females only 20, although more female subjects were tested than males. Of the abnormal levels observed, in the male the ratio of the number of those in the range above 139 mg. per cent to those in the range 120 to 139 mg. per cent was two to one; the ratio was one to three in the case of the females. The fact that a slightly higher proportion of the males were in the group aged 50 and above than was the case with the females may have contributed to the finding of more frequent and greater impairment in the males.

TABLE IV. REDUCING SUBSTANCE IN URINE DURING GLUCOSE TOLERANCE TEST ON 180 SUBJECTS

TWO-HOUR BLOOD SUGAR LEVEL (MG. %)	TOTAL SUBJECTS IN GROUP	URINARY REDUCING SUBSTANCE	
		ABSENT	PRESENT
Below 120	124	106	18
120–139	27	17	10
Over 139	29	10	19

Urine Sugar.—Table IV presents the results of Benedict's test performed upon the urine voided two hours after the ingestion of the glucose. The two-hour blood sugar was frequently found elevated in the absence of glycosuria. On the other hand, reducing substance appeared in the urine during tests in which the blood sugar had fallen below 120 mg. per cent at two hours.

DISCUSSION

The technique which we have employed is relatively simple. We required our subjects to present themselves after an overnight fast and to make themselves available for observation for two hours. If the test were performed on subjects who had recently ingested food, we suspect that it would prove a less sensitive indicator of minimal impairment of carbohydrate metabolism; the experience of others suggests that in such instances the blood sugar level two hours after the administration of glucose would be lower than if the patient had been fasting initially.[15] The crucial measurement is a single blood sugar determination. The venipuncture required can also furnish blood for other studies commonly conducted during general medical examinations. The routine of the tests is standardized, although the identification of the exact blood sugar level which is to be regarded as abnormal is a subject of debate. Approximately half the patients manifesting elevation of the blood sugar level above 119 mg. per cent two hours after ingesting glucose excreted no sugar in the urine during that period. Other authors[6,7] have likewise reported that tolerance tests employing measurements of blood sugar disclose mild deviations from the "normal" which are not revealed by screening tests employing only urinalysis, such as that one of us reported upon previously.[5]

The procedure we describe permits the identification of a group of subjects who for one reason or another manifest a prolongation of the period of elevation of blood sugar after the feeding of glucose. We recognize that in some of our subjects the elevation of the blood sugar above normal may have been due to factors other than the characteristic metabolic defects of diabetes mellitus, such as very low dietary content of carbohydrate during the days immediately preceding the study[16] and emotional factors.[17] Hypertension, which was present in some of our patients, is associated with an impairment of carbohydrate metabolism,[18] the relation of which to diabetes is obscure. It is proposed that subjects identified, by a procedure such as we have employed, as manifesting possible impairment of carbohydrate metabolism, be followed, along with a group of those characterized as normal by the test, to determine what proportion will some day develop convincing manifestations of diabetes; there is a dearth of reports on the subsequent course of subjects demonstrated to manifest mild impairment of metabolism by carbohydrate load tests. Meanwhile, we have urged our patients manifesting two-hour sugar levels above 139 mg. per cent to avoid obesity and to have their blood and urine examined for the sugar content at yearly intervals.

SUMMARY

1. In order to identify subjects in whom there is minor impairment of the ability to metabolize glucose, we have employed the Folin-Wu technique to measure the venous blood sugar two hours after the ingestion of 100 grams of glucose.

2. During the course of diagnostic studies of ambulatory patients, we thus examined 180 subjects aged 40 years or more who manifested no sugar in the fasting urine and whose fasting blood sugar level was below 120 mg. per cent.

3. In 56 (31 per cent) of the 180 subjects, the blood sugar level two hours after the ingestion of the glucose exceeded 119 mg. per cent; in 29 of these 56 subjects it exceeded 139 mg. per cent.

4. Following the ingestion of glucose, elevation of the blood sugar above the accepted normal value frequently occurred without concomitant glycosuria.

5. Of these subjects in whom abnormal elevations of postprandial blood sugar levels were thus demonstrated, a greater proportion were overweight than was the case with those in whom the levels were normal.

6. It is suggested that subjects identified by this screening test as manifesting possible impairment of carbohydrate metabolism are subjects appropriate for repeated observation for further evidence of mild diabetes mellitus.

We are grateful to Mrs. Bernadette Minehart, Mrs. Florence White, and their associates in the clinical laboratory of the Private Outpatient Service and the chemical laboratory of the Hospital for their assistance in the performance of these studies. Dr. Clifford A. Bachrach, Statistician of the Hospital, gave advice on the statistical treatment of our data.

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VARIATION OF BASAL RESPIRATION WITH AGE

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(Received for publication July 11, 1955.)

IN AN investigation on respiration of patients with heart disease, for purposes of examining the hyperventilation tendency previously reported,[1-3] difficulty in assessing the degree of hyperventilation was found because of inadequate standards. It is known from previous data that lung volumes change with age,[4,5] and the respiratory response to exercise shows changes.[6] However, for evaluation of respiratory changes, normal basal respiration with its variability must be known for comparative purposes. Accordingly, a study was made of hospitalized patients (or suitable subjects in basal conditions) without cardiopulmonary disease, in conditions which were basal, the basal condition being chosen in order to eliminate complications of activity, mental disturbances, and food intake. A recent similar study has been made by Shock and Yiengst.[7]

METHODS

Expired air during a 5- or 10-minute interval was collected in a Douglas bag, using Douglas valves with a rubber mouthpiece, flexible tubing 1 inch in diameter, and a nose clamp. After collection of the expired air and mixing in the Douglas bag, duplicate samples were collected over mercury and analyzed by the Scholander[8] procedure for carbon dioxide and oxygen. The volume of expired air was measured with a calibrated gas meter. From these measurements minute volume and tidal volume were determined and computed at 37°C. saturated with water vapor at ambient pressure (BTPS). Oxygen consumption rate and carbon dioxide production rate were computed under standard conditions (STPD) i.e., 0°C., 760 mm. Hg pressure and dry. Coefficients of oxygen utilization and carbon dioxide production (also called ventilation equivalents) were computed. In these studies particular care was taken to make the measurements in the basal state. In the majority of measurements the apparatus for collection of air was carried to the bedside of the patient or subject before arising in the morning and before breakfast. In a few measurements where the subjects were hospital personnel living away from the hospital, these subjects on arrival

Supported by a grant from the Los Angeles Heart Association.

TABLE I. RESPIRATORY VARIABLES FOR NORMAL MEN IN THE BASAL STATE UNDER HOSPITAL CONDITIONS OF BED REST AND DIET GROUPED ACCORDING TO AGE DECADES

Decade	21–30	31–40	41–50	51–60	61–70		21–30	31–40	41–50	51–60	61–70
Group	A	B	C	D	E	Group	A	B	C	D	E
N	26	22	17	26	18	N	26	22	17	26	18
Age $\bar{X}$	27.9	34.8	43.7	56.7	64.0	OCR $\bar{X}$	125.4	123.8	129.1	123.9	113.8
σ	1.8	3.5	2.2	2.5	3.1	SA σ	12.3	16.8	16.3	18.7	21.6
Mx	30	40	49	60	70	Mx	144	151	162	155	156
Mn	23	31	42	51	61	Mn	90	74	100	74	65
RR $\bar{X}$	11.3	12.5	11.82	13.42	12.78	CPR $\bar{X}$	102.4	99.4	101.3	98.7	90.8
σ	2.67	2.83	2.69	2.71	2.33	SA σ	12.9	15.9	12.6	16.4	18.1
Mx	16	20	16	20	16	Mx	121	122	127	140	137
Mn	8	8	8	8	9	Mn	68	55	82	67	51
TV $\bar{X}$	304.7	296.7	297.9	295.6	294.9	O_2Cf $\bar{X}$	39.42	37.53	38.05	32.87	31.86
σ	65.8	56.5	52.7	71.8	63.2	(H-C) σ	5.38	3.96	6.05	5.54	4.94
Mx	410	433	425	483	445	Mx	55.6	44.1	52.1	47.5	42.8
Mn	199	232	221	177	155	Mn	29.1	31.4	28.3	26.1	24.38
MV/SA $\bar{X}$	3.21	3.37	3.47	3.87	3.64	O_2Cf $\bar{X}$	2.58	2.72	2.68	3.12	3.22
σ	.47	.56	.75	.78	.79	(A-K) σ	.30	.26	.39	.48	.48
Mx	4.07	4.64	5.09	5.90	5.34	Mx	3.44	3.26	3.52	3.83	4.01
Mn	2.39	2.05	2.35	2.63	2.42	Mn	1.80	2.27	1.92	2.11	2.34
Exp.CO_2 $\bar{X}$	3.94	3.70	3.69	3.24	3.14	CO_2Cf $\bar{X}$	31.95	29.39	29.81	26.00	25.37
σ	.39	.39	.47	.44	.42	(H-C) σ	3.31	3.56	4.33	3.53	3.62
Mx	4.76	4.33	4.91	4.04	4.02	Mx	38.5	35.0	39.80	32.5	32.5
Mn	3.04	3.04	2.89	2.36	2.36	Mn	24.0	22.87	23.3	18.85	19.1
pCO_2 $\bar{X}$	27.97	26.18	26.13	23.00	22.20	CO_2Cf $\bar{X}$	3.17	3.42	3.41	3.96	4.02
σ	2.71	2.77	3.4	3.06	3.14	(A-K) σ	.3995	.399	.412	.561	.560
Mx	33.6	30.7	34.65	28.6	28.4	Mx	4.15	4.07	4.28	5.30	5.24
Mn	21.6	21.5	20.5	16.68	16.7	Mn	2.60	2.85	2.52	3.08	3.08
HPR $\bar{X}$	36.4	35.8	36.3	35.8	32.9						
σ	3.8	4.8	4.7	5.4	6.2						
Mx	41.6	43.6	46.9	44.8	45.2						
Mn	26.1	21.4	28.9	21.4	18.8						

(For key to symbols, see footnote on opposite page.)

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at the hospital without breakfast were allowed to rest thirty minutes and the measurements were taken in the supine position after the rest. The nonhospitalized subjects were all men, mostly hospital attendants, interns, or residents living in bachelors' quarters in the hospital dormitories. These normal subjects were mostly in the younger age groups. The older groups included ambulatory patients without clinically evident cardiac, respiratory, or systemic disease and were mainly from the Surgical Service. These subjects were nearly all selected by the same person, following review of their hospital records and a brief interview with an examination of their hearts and chests. All had routine hospital laboratory studies, including an electrocardiogram if the subject was over 40 years of age. Any question of abnormality in any of these examinations excluded a subject from this study. This group then represents "normal" subjects as accurately as can be determined by clinical evaluation.

RESULTS AND DISCUSSION

The summarized data are collected in Table I. The patients were divided into groups corresponding to decades commencing with the 21-30 year age group (A) and extending to the 61-70 year age group (E). For each group the variables measured were (1) respiratory rate (RR) in breaths per minute; (2) tidal volume (TV) in milliliters per square meter of body surface BTPS; (3) minute volume of respiration (MV) in liters per minute per square meter of body surface; (4) carbon dioxide in expired air (Exp. CO_2) in percentage of CO_2 in dry expired air; (5) the tension of CO_2 in millimeters of mercury (pCO_2) in expired air saturated with water vapor at 37°C.; (6) oxygen consumption rate (OCR) in milliliters of O_2 at 0°, 760 mm. Hg dry, i.e., STPD, per square meter of body surface per minute; (7) carbon dioxide production rate (CPR) in milliliters of CO_2 under the same conditions, i.e., STPD; (8) the coefficient of oxygen utilization designated as the Herbst-Cournand (H-C) coefficient and defined as the milliliters of O_2 STPD removed from 1 liter of expired air BTPS and the similar coefficient for CO^2; (9) the so-called ventilation equivalents for oxygen and carbon dioxide designated as the Anthony-Knipping (A-K) coefficients and defined as the number of liters of expired air, BTPS, for each 100 ml. of O_2 consumed or CO_2 produced; and (10) the heat production rate in Cals/M^2 hour. For each variable there was determined the mean ($\bar{X}$), and the standard deviation (σ) as defined by Snedecor,[9] the range including the maximum (Mx) and the minimum (Mn).

N, Number of men in each subgroup; RR, respiratory rate; TV, tidal volume in milliliters; BTPS per square meter of body surface; MV, minute volume of respiration, L. BTPS per minute, per square meter of body surface; Exp. CO_2, CO_2 percentage of dry expired air; pCO_2, tension of CO_2 in the expired air at 37° C. saturated with water vapor; OCR/SA, oxygen consumption rate in milliliters dry oxygen at 0° and 760 mm. pressure, STPD, per square meter of body surface; CPR/SA, carbon dioxide production rate in the same units; O_2 Cf. H-C, the Herbst-Cournand coefficient defined as the milliliters of O_2 STP removed from 1 L. of expired air BTPS; CO_2 Cf. H-C, the Herbst-Cournand coefficient for CO_2 in the same units; O_2 Cf. A-K, the Anthony-Knipping coefficient for oxygen defined as the minute volume BTPS for each 100 ml. of O_2 STPD consumed; CO_2 Cf. A-K, the same coefficient for CO_2 in the same units; HPR, heat production rate in Cals./M^2 hour. $\bar{X}$ is the mean for each group, σ is the standard deviation, Mx the maximum value in each group and Mn the minimum value.

Using the mathematical methods of analysis of variance, the significances of any trends with age were determined. For the classification into subgroups by decades the F value was determined where $F = f_1/f_2$. f_1 is the subgroup variation among the classes, i.e., $f_1 = \Sigma Ni(\bar{x}i - \bar{x})^2/n-1$, and f_2 is the group variation within the classes, i.e., $f_2 = \Sigma(x - \bar{x}i)^2/N-5$. In these formulae x is the value of each individual variable, $\bar{x}i$ is the mean for each subgroup, $\bar{x}$ is the mean for the entire group, n is the number of subgroups, Ni is the number of individuals in each subgroup, and N is the total number of individuals. The values of F for each variable and the probability of nonsignificance (p) were computed.

Respiratory Rate, Minute Volume and Tidal Volume.—The basal respiratory rates ranged from 8 to 20, with mean values of 11 to 13. The mean tidal volumes for each group were in the approximate range of 290 to 310 ml./M^2 BTPS with individual values ranging from approximate values of 200 to 450 ml./M^2. There was no significant change of respiratory rate or tidal volume with age with p values (probability of nonsignificance) exceeding 0.01. The minute volume of respiration, measured as liters BTPS per square meter of body surface, ranged for group means from 3.2 to 3.9 approximately and showed a slight but definite trend to increase with age. In general, the minute volume of the older age groups (D and E) was approximately 20 per cent above the younger age group (A), this increase having a p value less than 0.01.

The values of basal minute volume reported here are in the same general range as similar values found by Baldwin, Cournand, and Richards,[10] i.e., 3.1 to 3.9 L. (BTPS) per square meter per minute. These investigators, however, found their minimum minute volume of 3.1 L. (BTPS) per square meter for an age group of 37 to 49 years, while both younger and older age groups had higher minute volumes. Shock and Yiengst found the minute volume (STPD) for men in the age group 40-49 to have a mean value of 3.97, and for the age group 50-59 to be 4.03. If these values are increased 20 per cent to convert to BTPS for comparative purposes, it is apparent that the values of Shock and Yiengst are considerably higher than those reported here or the values of Baldwin and associates. This may have been owing to the difference in procedure, since Shock and Yiengst used a mask, while the other two groups used mouthpieces. In the older groups (mean age 61, range 51 to 75 years) Greifenstein, King, Latch, and Comroe[4] found a resting minute volume of 6.1 L./min.M^2 and a mean respiratory rate of 19/min., values higher than those of our study or that of Baldwin, Cournand, and Richards, or Shock and Yiengst.

Carbon Dioxide in Expired Air.—The carbon dioxide in expired air (mixed dead space and alveolar air) was measured in two ways as (1) percentage of dry expired air and (2) tension, in millimeters of mercury, in gas at 37° C. saturated with water vapor, using the formula $pCO_2 = (\%\ CO_2) \times (B-47)$ where B is the ambient barometric pressure. There is a statistically significant downward trend of CO_2 in expired air with age. The pCO_2, in millimeters of mercury, declines from a mean of 27.97 in the youngest age group (A) to 22.20 in the oldest group (E), a decrease of approximately 20 per cent. The individual values of pCO_2 as a function of age are plotted on the graph of Fig. 1. A linear regression

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formula relating pCO_2 to age was obtained by the method of least squares and the formula is $pCO_2 = 32.02\text{-}0.153 \times \text{age} + 3.3$ the variation of 3.3 being the standard error of the estimate.

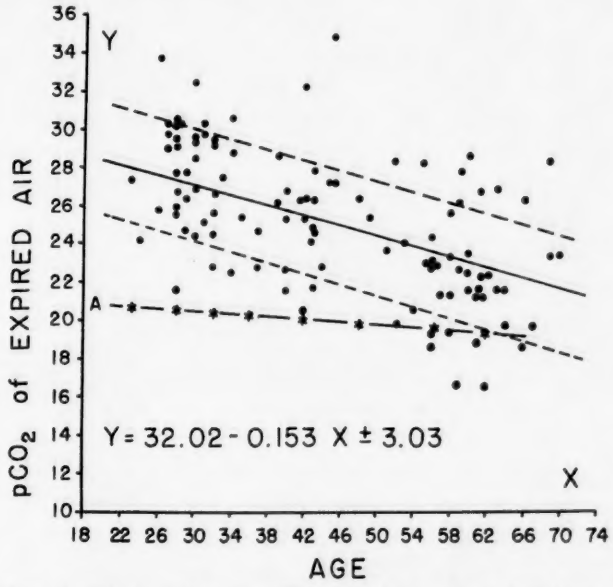

Fig. 1.—Values of pCO_2 in expired air, millimeters of mercury, plotted for various age groups. A linear regression formula obtained by the method of least squares is plotted by the continuous straight line and the equation for this straight line is given. The broken line on each side represents the limits of the standard error of the estimate. The line A, with values in crosses, is drawn from data obtained by Boyer and Bailey.[1]

In a similar study conducted by Boyer and Bailey,[1] pCO_2 of expired air as a function of age was determined. However, the values of pCO_2 obtained by these investigators were considerably below the values obtained in the present study. A decline of pCO_2 with age was also found by Boyer and Bailey, but the slope of their line was less as is shown in Fig. 1. On seeking the cause for the difference in pCO_2 values between the data of Boyer and Bailey and the data of the present study, the following explanation is suggested. Boyer and Bailey[1] used a face mask with valves for collection of expired air, whereas in the present study a mouthpiece with Douglas valves was used. Gray[11] has criticized the technique of Boyer and Bailey with respect to large instrumental dead space, since their mask method involves a large dead space necessitating rebreathing of expired air with an excess of CO_2. This would cause hyperventilation resulting in an abnormally low pCO_2 in expired air. The mouthpiece with the Douglas valve as used in the present study has much less dead space than a mask.

Oxygen Consumption Rate (OCR) Carbon Dioxide Production Rate (CPR), and Heat Production Rate (HPR).—The oxygen consumption rates and carbon dioxide production rates in milliliters (STPD) per minute (standard conditions of 0°C., 760 mm. Hg pressure and dry) per square meter of body surface for various age groups are given in Table I and oxygen consumption rates are plotted

in Fig. 2, and on the same graph are given similar data obtained from the tables of Robinson,[5] Boothby, Berkson, and Dunn,[12] Robertson and Reid,[13] Fleisch,[14] Shock and Yiengst,[7] Lewis,[15] and Matson and Hitchcock.[16] The values of oxygen consumption rate for various age groups, both those reported here and other values in the literature, in general, lie in a range between two limits, namely an upper limit represented by the data of Boothby, Berkson, and Dunn[12] and a lower limit represented by the data of Robertson and Reid.[13] Such a range is the expected when the experimental conditions of measurement are considered. The measurements of Boothby, Berkson, and Dunn were obtained from the first (and only) measurement made on each person, as was customary in the clinical

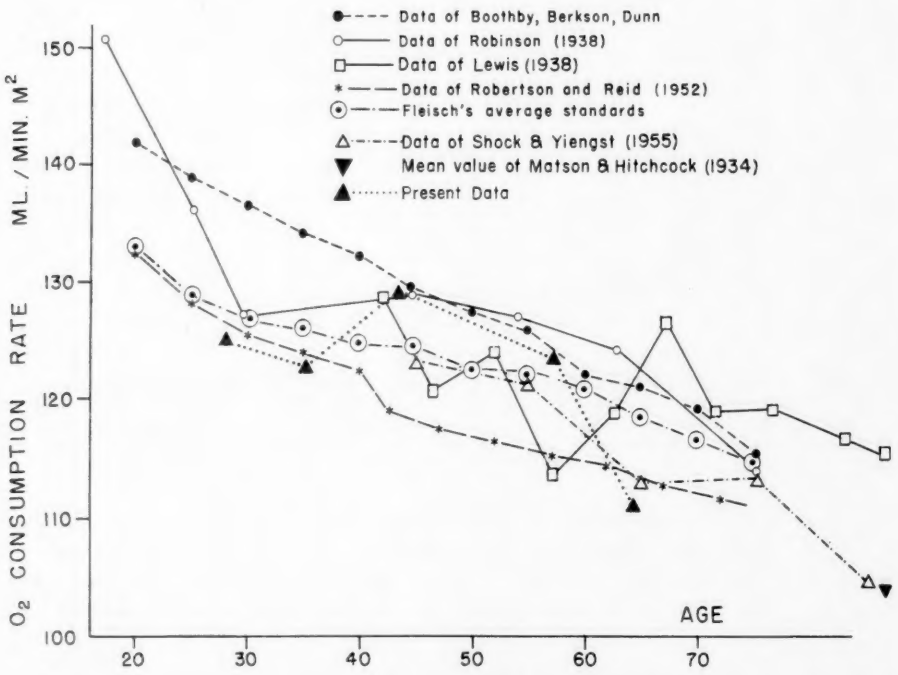

Fig. 2.—Oxygen consumption rate of men of various age groups. Oxygen consumption rate is measured as milliliters of O_2 (standard conditions 0°C., 760 mm. Hg pressure, dry) per square meter of body surface per minute. Comparative data from the papers of Robinson,[5] Boothby, Berkson, and Dunn,[12] Robertson and Reid,[13] and Fleisch[14] are given.

measurement of basal metabolic rate. The values of Robertson and Reid were obtained from a series of measurements in which each measurement was repeated until successive determinations differed by less than 5 per cent, and the lowest value was chosen. In our data for the five age groups, three of the groups, namely A, B, and E, differed insignificantly from the data of Robertson and Reid. Two of the groups, C and D, were higher, almost reaching the values of Boothby and associates. There may be a tendency of uncertain statistical significance for the decrease of oxygen rate with age to have a slope lesser in the middle age group than in the younger and older age groups. Such a tendency is shown by

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the data of Robinson,[5] the average standards of Fleisch,[14] and our data, but not by the values of others. There is, however, a downward trend of oxygen consumption rate with age in agreement with others and an agreement with the recent statement of DuBois[17] that "for many years it has been obvious that the older standards (basal metabolic rate) were set at levels which were too high." For comparison with other data in the literature, heat production rate values in kilogram calories per square meter per hour have been computed from oxygen consumption rates by the customary basal metabolic rate method. (Table I.)

Ventilation Equivalent.—In 1928 Herbst defined a quantity termed the utilization coefficient for oxygen, which was the ratio of oxygen consumption rate (milliliters per minute) to minute volume of respiration (liters per minute). This ratio gives the volume of oxygen removed from 1 liter of air expired and is a measure of respiratory efficiency, since the greater the efficiency of respiration the more oxygen is removed from a liter of respired air. A similar coefficient is defined for carbon dioxide production. In 1930 Anthony[18,19] introduced the term "ventilation equivalent for oxygen" which he defined as the volume of air breathed (expired) from which 100 ml. of oxygen were removed. This ratio may be used as a measure of hyper- or hypoventilation, since this ratio increases with hyperventilation and decreases with hypoventilation. In the past two decades since those terms were first defined, these two coefficients have been determined frequently for both normal individuals and patients. In general, the European investigators prefer to use the ventilation equivalent of Anthony which will be designated here as the Anthony-Knipping coefficient since its first extensive study was made by Knipping and Moncrieff.[20] The group of workers associated with Cournand[10] have preferred the Herbst ventilation equivalent which will be here designated as the Herbst-Cournand coefficient. The term "oxygen removal ratio" has also been used for this ventilation equivalent (Kory and associates[21]). One ratio, except for the factor of 100, is the reciprocal of the other. In the physiologic and clinical literature considerable uncertainty has prevailed concerning the temperature-pressure corrections for this ratio. The earlier workers used solely spirometer values for both oxygen consumption rate and minute volume, ignoring pressure and temperature. But, more recently, BTPS values have been used. Since it is customary to express oxygen consumption rate (OCR) and carbon dioxide production rate (CPR) under standard conditions of 0°C., 760 mm. Hg and dry, STPD, and minute volume of respiration (MV) at 37°C., ambient pressure and saturated with water vapor, BTPS, these standardized values will be used here. The values will be computed according to the following formulas:

Anthony-Knipping coefficient (A-K coefficient)

$$\text{For } O_2 \quad \frac{100 \times \text{MV (L./min. BTPS)}}{\text{OCR (ml./min. STPD)}}$$

$$\text{For } CO_2 \quad \frac{100 \times \text{MV (L./min. BTPS)}}{\text{CPR (ml./min. STPD)}}$$

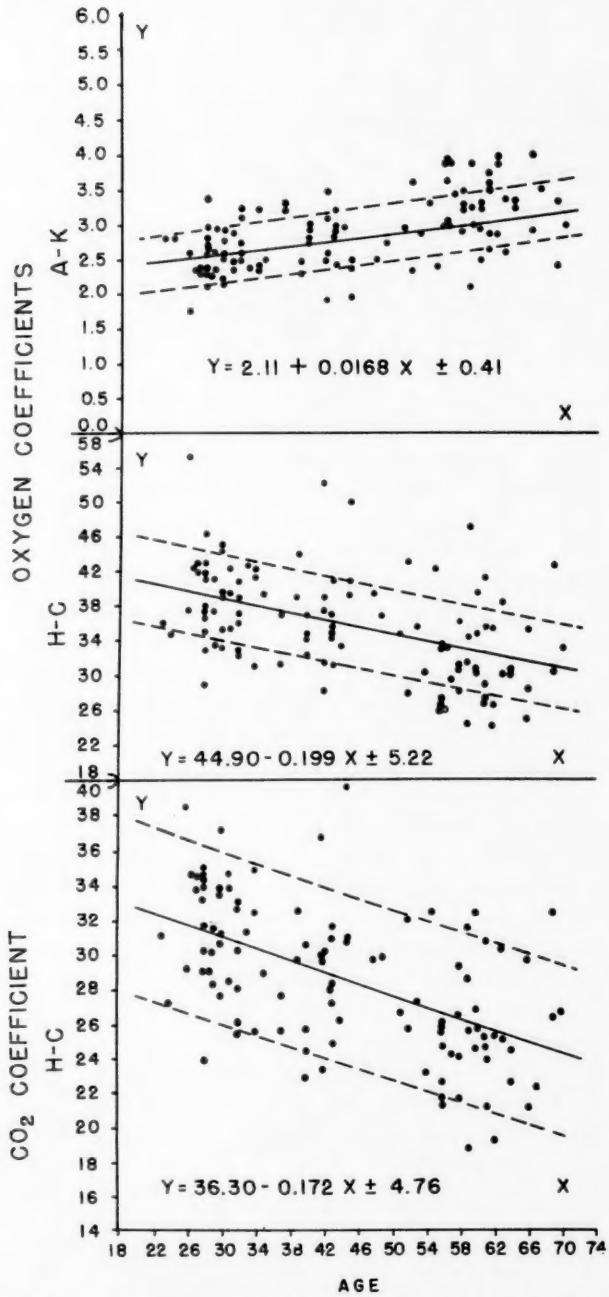

Fig. 3.—Ventilation coefficients for oxygen and carbon dioxide. The A-K coefficient is the Anthony-Knipping coefficient defined by the ratio $100 \times MV/OCR$ for oxygen. The H-C coefficient is the Herbst-Cournand coefficient defined by OCR/MV. OCR is oxygen consumption rate as milliliters of O_2 (STPD) per minute, and CPR is carbon dioxide production rate in the same units. MV is the respiratory minute volume measured by liters (BTPS) of expired air per minute. The formulas are linear regression formulas and the dotted lines give the limits of the standard errors of the estimates.

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Herbst-Cournand coefficient

$$\text{For } O_2 \quad \frac{\text{OCR (ml./min. STPD)}}{\text{MV (L/min. BTPS)}}$$

$$\text{For } CO_2 \quad \frac{\text{CPR (ml./min. STPD)}}{\text{MV (L./min. BTPS)}}$$

If desired to change OCR and CPR from standard conditions STPD to conditions BTPS, these rates can be multiplied by the factor $310 \times 760/273 \times$ (B-47) which for barometric pressure, B, of 760 mm. Hg equals 1.21. These four coefficients with means for each age group and standard deviations are given in Table I. Each coefficient undergoes a significant change with age (p is less than 0.001), the A-K coefficients decreasing and the H-C coefficients increasing. These results indicate a lessened efficiency with advancing age or a tendency to hyperventilate. For normal men of various ages, other investigators found the following values: Kaltreider and McCann[22] measured the ventilation equivalent of Anthony and Knipping at "standard temperature" and found a value of 2.40 L. per 100 ml. Knipping and Moncrieff[20] found a mean value of 2.44, while Hurtado and Boller[23] a value of 2.66, and McMichael[3] a value of 2.49. Making the correction cited above to reduce both gas volumes to BTPS, our mean value for the younger age group is by comparison 2.12 L. per 100 ml., indicating that the subjects reported here had a somewhat more efficient ventilation or less of a tendency to hyperventilate. The CO_2 coefficients indicate a definite downward trend with advancing age. The carbon dioxide added to 1 liter of respired air (the H-C coefficient) decreased from the mean value of 31.95 in the younger group to 25.37 in the older group. This indicated that the oldest group needed approximately 20 per cent more ventilation than the youngest group for removal of the same amount of CO_2. This is also shown by the A-K CO_2 coefficient where for elimination of 100 ml. CO_2 STPD 3.17 L. of air was breathed for the youngest group, but the oldest group breathed 4.02 L. to remove the same amount of CO_2. This hyperventilation tendency is also demonstrated by the values of pCO_2 in expired air, a value closely related to the H-C coefficient.

The "scatter diagrams," giving the individual values of the coefficients, are shown in Fig. 3 together with linear regression formulas and lines showing the limits of the standard error of estimate. These formulas can serve as prediction formulas to determine the probable value of the coefficient for a patient if he were normal.

In summary, the results of this study indicate that with advancing age the respiration of normal individuals in a basal state under hospital conditions of rest and diet has the following characteristics: (1) no significant changes in tidal volume or respiratory rate, (2) a slight rise in respiratory minute volume, (3) a decline in oxygen consumption rate agreeing with previous work, (4) a reduction of the CO_2 in expired air indicated by the pCO_2 value, (5) a reduced efficiency of ventilation of approximately 20 per cent as measured by the amount of air breathed for the elimination of a constant amount of carbon dioxide or the utilization of a fixed amount of oxygen.

The technical assistance of Nathan Elder, medical chemist, and Eileen Stolzis, medical statistical librarian, is gratefully acknowledged. For advice on statistical problems we are indebted to Dr. Daniel Simmons. The work was made possible by the aid and cooperation of Dr. Ben Klaumann, Chief of the Pulmonary Function Laboratory, Long Beach Veterans Hospital, where the work was performed, and by financial assistance from the Los Angeles Heart Association and the Long Beach Heart Association.

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REHABILITATION OF THE ELDERLY PATIENT WITH PINNED FRACTURE OF THE HIP

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ALTHOUGH studies of the blood circulation of the upper part of the femur[1] have produced a better understanding of the factors underlying healing, nonunion, or aseptic necrosis after fractures of the hip, we still lack a generally accepted policy in the postoperative management of this disorder. Different methods are advocated and employed. Early ambulation,[2] made possible by Smith-Peterson nailing and its modifications, has been opposed by advocates[3,4,5] of rigid immobilization of the fracture parts and avoidance of early weight-bearing.

The following method of management is a "middle-of-the-road" course which seems to be receiving increased acceptance and approval. The basic concept includes: (1) meticulous diagnostic evaluation and reconditioning of the patient's total health; (2) early limited weight-bearing to facilitate crutch walking and to make it feasible and safer for the elderly patient; and (3) late full weight-bearing.

MEDICAL EXAMINATION

Many elderly patients have good medical reasons contributing toward the imbalance which may have lead to a fall and consequent fracture of the hip. Unfortunately the reason for the fall is not always ascertained by the examiner. The more usual causes of such falls and resultant fractures will be enumerated here.

1. *Anemia.*—A hemoglobin level of 12 Gm., in the elderly patients is much too often erroneously considered normal. The older patient requires the same hemoglobin level as that of the average adult population. Even a moderate degree of anemia may be responsible for inadequate supply of nourishment to the central nervous system, resulting in inadequate coordination of locomotion. Under such circumstances, every attempt should be made to determine the reason for the low hemoglobin level, and it should be effectively treated concomitantly with efforts to ambulate the patient.

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2. *Disorders of Circulation.*—Mild heart disease, compatible with a quiet life, may nevertheless be hazardous by producing temporary cerebral hypotension with loss of equilibrium.

3. *Osteoporosis.*—This may be caused by locomotor disuse, nutritional deficiency, or endocrinologic disturbances.

4. *Neurologic disorders.*—A patient who has suffered a fractured hip deserves a thorough neurologic examination to exclude disorders which may be emenable to treatment or other detectable disturbances which may lead to specific instructions for safeguards in walking.

5. *Poor Reflex Adjustment of Peripheral Circulation.*—On abrupt change from a sitting to a standing position, a sudden drop of the blood pressure occurs, which, in younger persons, is normally adjusted in a reflex manner within a fraction of a second. This reflex readjustment and restoration to adequacy may be delayed in some elderly patients, thereby producing complaints of dizziness with sudden change from a lying or sitting position to the erect posture. (Such a patient should be taught to wait a few seconds after standing up before walking.)

6. *Impaired Righting Reflexes.*—Many old people lose their balance when they hyperextend the neck, as, for instance, while reaching for something from a high shelf.

Dr. Jan H. Bruell and I are investigating disorders of visual space perception in normal elderly people and of patients with locomotor disabilities such as hemiplegia and Parkinsonism.

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PREAMBULATION TRAINING

After a patient has regained consciousness postoperatively, he should be encouraged to move actively (bend and straighten) the injured leg in bed unless there are special contraindications. If the weight of the bedcovers hampers his activity, a cradle is inserted beneath the covers at the foot of the bed. If the soft-tissue injuries around the site of the fracture produce enough pain or discomfort to impede active flexion and extension of the hip and knee, the physical therapist should assist in these active movements. Passive flexion and extension of the hip should be avoided at all costs.

I am convinced that routinely no other exercises around the involved hip are indicated or needed for the average old person. The functional management of the patient as described herein is adequate to prepare for the daily requirements of his future life. Especially in old people (except when specifically indicated), adduction, abduction, and external and internal rotation exercises with the involved hip should be omitted routinely during the entire period of postoperative management.

The average patient may be allowed to sit in a wheel chair and start exercises within twenty-four hours postoperatively. The nursing staff must be trained to assist and properly instruct him in the techniques of transferring from his bed to the wheel chair, putting his weight on the good leg and both arms. The nurse must be sure that the patient uses this same supportive technique in transferring from the wheel chair to a toilet seat. The nurse must also be trained

to assist the patient in helping himself in and out of a bathtub without injuring the site of the operation on the fracture.

The guiding principles during the first phase of preambulation and ambulation training are: (1) restoration of the general health of the patient; (2) functional activities to improve the power of both upper extremities and the good leg; and (3) limited weight-bearing and active range of motion exercises for the involved extremity. The functional approach of such exercises as standing up with full weight-bearing on the good leg not only improves the performances of the uninvolved joints and muscles, but also allows us to provide the patient with supervised training directed toward the maintenance or improvement of postural reflexes and cardiovascular adjustment to the requirements of erect posture.

The exercises which must precede crutch walking, using a three-point gait with limited weight-bearing on the involved leg, are graduated carefully. The two main stages preceding the training on crutches are independent standing up on the good leg, with only slight tiptoe weight-bearing on the involved leg; and walking between parallel bars with this same limited weight-bearing.

The standing-up exercises give us the first information as to the probable rate of progress leading to crutch walking in each particular case. A patient who is able to stand up without assistance on the first day will often progess quickly from walking between the parallel bars to walking outside them. Some patients need assistance in getting up to a standing position for a few days, and the physical therapist is needed for skillful teaching in order for the patient to reach the stage of being able to stand without assistance. The exercises leading to this goal are described elsewhere[5] as graduated standing-up exercises. The main principle of graduation is that in the early phases of training the sitting position should be as near that of standing as possible. The patient begins the exercises sitting high in a chair, either upon a special high seat or on firm pillows, with the knee of the good leg almost straight and the chair at a full arm's length from the rail. Provision must be made in front of the patient's good leg in order to prevent him from slipping forward while he attempts to stand up. He pulls himself up with a straight or almost straight knee, analogous to a baby during his first days of pulling himself up to a standing position. As standing-up training progresses, the knee, in the starting position, is gradually flexed more by diminishing the height of the seat and by moving the chair closer to the rail. Thus the patient will gradually reach a full sitting position. Assistance is provided at the beginning of every stage, and the height of the seat is not diminished until the patient is able to stand up without assistance from the given level of seat from which he is currently attempting to rise.

Concomitantly with these precrutch exercises, the patient is instructed in power-building exercises for the upper extremities. Push-ups are the best power-building exercises for these extremities.

During preambulation training, the careful therapist and the supervising physician ought to have many opportunities to observe whether the change from a sitting to a standing position itself produces complaints of dizziness or locomotor incoordination. One of the most frequent findings is the elderly patient's tendency to lean backwards while standing or while holding on to the rail.

The patient with a fractured hip who is doing well in independent standing on one leg is allowed to proceed with walking between the parallel bars with limited weight-bearing on the involved leg.

LIMITED WEIGHT-BEARING

I shall avoid a theoretical discussion of whether limited weight-bearing (1) is dangerous for the fracture site[3] or (2) improves its healing,[6] because I am convinced that there are no consistent data on which to base such a discussion. My clinical impression is strongly in favor of using limited weight-bearing as a routine procedure for an elderly patient with a fractured hip. Limited weight-bearing for the average patient seems to have no deleterious effect on the maintenance of the alignment of the fracture site, except in a few instances, in which I am careful that the particular patient has enough insight and perseverance to execute limited weight-bearing properly. These are the main instances in which extreme caution is required: (1) A comminuted intertrochanteric fracture where too much weight-bearing could produce a collapse of the fragment or fragments between the proximal and distal parts of the fracture. Such a collapse often pushes the tip of the nail into the acetabulum. (2) A fracture of the neck with the fracture line nearly parallel to the longitudinal axis of the shaft of the femur which would possibly permit shearing of the weight of the proximal fragment on the distal fragment of the fractured bone. (3) A subcapitular fracture which, under too much weight-bearing, could result in a collapse of a united, but necrotic, femoral head.

Slipping of the proximal part of a nailed fracture[6] should not be an argument against limited weight-bearing. It usually occurs (1) when the original malalignment was not corrected adequately during or preceding the operation; (2) when full weight-bearing was permitted too early; or (3) in cases in which slipping of the proximal part of the nailed fracture would have occurred even if the patient had been kept in bed.

Limited weight-bearing means that the patient is allowed to tiptoe with the involved leg while weight-bearing is done by the arms and shoulder depressors on crutches (three-point gait), or, during the precrutch training period, by the hands on parallel bars. This touching of the tip of the toe to the floor allows the patient to have adequate balance, which is particularly essential in the aged.[7] Everyone who has tried to teach an elderly person with a fractured hip to walk on crutches while keeping the involved leg in the air will appreciate the advantages of allowing the patient to touch the floor with his toes to maintain his balance. Tiptoe crutch walking is graduated through the phases of independent standing up, and later of independent walking between the parallel bars, with the pattern of a three-point crutch walk with limited weight-bearing. On many occasions I have observed patients with maximally comminuted intertrochanteric fractures which were neither nailed nor plated and which, on repeated radiologic examination, did not show a change of alignment of the multiple fragments at the fracture site when the patients were allowed to walk under careful training and supervision with limited weight-bearing on the tiptoe of the involved leg and using crutches as described above.

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THE THREE-POINT CRUTCH WALK

The classical three-point crutch walk[8] with limited weight-bearing is performed in such a way that the patient, standing on the good leg and tiptoeing with the involved leg, puts both crutches forward simultaneously, then advances the involved leg, putting the toes of the involved leg close to the line in between the crutches, and, putting the weight of his body on the crutches, swings the good leg through. In old people this classical three-point gait will be subject to many modifications. Some patients prefer to move the crutches separately, a method giving them more control of their movements. I do not oppose this tendency if the patient does not feel safe in advancing both crutches simultaneously. Many patients do not produce a swing-through of the good leg, but rather do a very short jump of the good leg without crossing the line between both crutches (swing-to). I see no reason for forcing a debilitated person to do a swing-through as long as he does not feel safe in so doing.

The classical requirements for crutch walking are that the patient puts the weight of his body through his hands on the handrest of the crutch. Old people ought to be allowed to put part of their weight through their axillae on the armrest of the crutch in addition to the weight borne by their hands on the crossbar. This increases stability and ability to balance. Although, theoretically, crutch paralysis could be produced in this manner, I have not had a single case of crutch paralysis in old people. The armrest must be provided with a foam-rubber cover when used in this way. The length of the crutches must be properly measured,[8] very often having to be shorter than would be required for a young adult of the same height; and the tip of the crutch should have a wide suction cap attached.

I favor conventional wooden crutches for elderly patients. The contraindication to Loftstrand crutches is the confusion these patients often show when confronted with a reversed forearm piece.

Some patients automatically use the intermittent double-step gait[9] while others should be taught to use it. In this type of gait the patient momentarily stops after every second step with the good foot in a forward position, in order to regain his balance and continue walking.

The transition from walking between parallel bars to walking on crutches is often uncomplicated. If the patient has major difficulties in relying upon the crutches for balance and weight-bearing, he can progress through exercises of balancing from a wall. He leans his back against the wall,[10] puts his crutches one and a half feet in front of himself, and then puts his body weight on the crutches. He is able to return to the wall at any moment for support and, while leaning against the wall, is able to lift the tips of the crutches off the floor. Thus the patient intermittently learns to put the weight of his body on the crutches at almost the instant the tips of the crutches touch the floor, and then is able to return to the safety of the supporting wall.

Some physicians almost routinely provide patients with a fractured hip with an ischial weight-bearing caliper. My experience with these in elderly patients has been disappointing. They are very good in selected children or

able-bodied adults, but markedly interfere with the walking performances of aged patients. A well-fitting caliper should have a half-inch allowance inside the shoe between the bottom of the heel and the insole. This provision is necessary to allow for the give of the soft tissues near the ischial weight-bearing ring. They give way under weight-bearing, and the femur of the involved leg is pushed down. If this shoe allowance is not provided, the patient will put weight on the bones of his lower extremity and not through the caliper. Even a perfectly fitted ischial weight-bearing caliper is extremely uncomfortable for an elderly person. Inability to shorten the involved leg during the swing phase, due to the stiffness of the caliper at the knee, is a factor which adds to the otherwise poor balance of the elderly patient.

No training for crutch walking is complete unless the patient is taught to go up and down stairs.[10] If a rail is available, the patient puts both crutches in the opposite hand, climbs to the next higher step with the good leg, and follows with the involved leg and the crutches. Ascending the stairs is always done by using the good leg to elevate the body. Descending the stairs is done by bending the good leg while the involved leg and the crutches are placed on the next lower step.

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It is essential that during the patient's period of training for crutch walking he should be in a low hospital bed from which the casters have been removed to provide stability. This enables the patient to learn to get up from a bed similar to his own at home. Elderly patients with hip fracture often have difficulty in getting up from a conventional toilet seat unassisted. A rehabilitation and/or surgical ward should have provisions for an elevated toilet seat and a grab bar to enable them to be as independent as possible.

A home evaluation should be made before the patient is discharged from the hospital. This includes suggestions for removing small scatter rugs, arranging bathroom and toilet facilities according to the rules accepted in "Activities of Daily Living" training, and special attention to the rearrangment of objects in the kitchen and other rooms to avoid the necessity for reaching up to high shelves. This type of reaching for something placed on a high shelf is often responsible for the patient's losing balance and falling backward. A properly trained therapist or social worker can give the patient and his family many practical suggestions for rearranging the kitchen along the lines accepted for cardiac patients[11] to insure economy of physical effort.

FULL WEIGHT-BEARING

I favor routine late full weight-bearing. An x-ray picture is made at least once a month, and full weight-bearing is allowed according to the results of this and the type of fracture of the hip (Christophe[12]). I allow full weight-bearing usually only after four or five months of walking on crutches; and, in particular cases, for example in some subcapitular fractures, the patient is encouraged to continue the three-point crutch walk with limited weight-bearing for much longer periods, sometimes as long as two years.

The patient can be discharged home, or to homelike surroundings, as soon as crutch walking is done safely. He is then followed up at an outpatient clinic.

Occasionally, follow-up at home by the physical therapist is indicated to check the results of the original home visit and to ascertain whether the patient is able to carry over to his home conditions all the activities of daily living training he received while at the hospital. A patient who learned to climb stairs while at the hospital will often find it difficult to climb his own stairs unless he is encouraged and, for a short period of time, assisted in so doing.

Once full weight-bearing is allowed, the patient should be given an opportunity to discontinue gradually the use of crutches in a supervised manner. Many old people prefer to graduate from crutch walking to one cane through a period of walking with two canes in a manner similar to that of crutch walking. Theoretically, one cane is used in the hand opposite to the side of the fractured hip if its main purpose is to assist in balancing. It is used in the hand on the same side as that of the fractured hip if its main purpose is support for weight-bearing. The physical therapist and the supervising physician should give the patient several trials to decide which hand the single cane should be carried in for each particular case. Sometimes the carry-over from crutches to canes is prolonged because the patient has major psychologic difficulties in adjusting himself to walking without crutches. Canes used by elderly patients should have thicker handles than those used conventionally, and broad rubber suction tips are always indicated.

Physical therapy should not be discontinued until a permanently safe walking pattern has been established.

The author wishes to express his sincere appreciation to Dr. Marjorie Warren, Geriatric Unit, West Middlesex Hospital, Middlesex, England, for introducing him to the problems of the geriatric patient; to Dr. Howard Rusk and his associates, Dr. Michael M. Dasco, and Dr. Hans Kraus, Department of Physical Medicine and Rehabilitation, New York University, for valuable suggestions and constructive criticisms; and to Dr. David R. Weir, Medical Director, Highland View Hospital, Cleveland, Ohio, for providing an atmosphere encouraging toward research in chronic diseases.

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Editorials

PROGRESS AND FUTURE PLANS OF THE FEDERAL VOCATIONAL REHABILITATION PROGRAM

Chronic disease is one of the major causes of dependency in this country. The losses, in dollars and in social distress, growing out of neglected chronic disability, probably never will be adequately totaled, yet they leave their mark on the face of every community in our land.

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Consider this one staggering fact: about a half billion dollars of local, state, and Federal funds are being paid out annually in public assistance to support around one million people, including 325,000 dependent children, *because of prolonged disability* of the family breadwinner. Every taxpayer shares that cost, which is only one segment of the total expense which chronic disability imposes upon us.

Among these individuals are several thousands who could be rehabilitated—some to mobility and employment, some to self-care at home or in the hospital. The potential savings are enormous.

In an effort to explain why our society, so advanced in so many respects, should give so little of its present attention and resources to restoring these people, one needs to fully appreciate the forces which have been at work for the past two decades. Today's great skills in the medical sciences, so far advanced over a few years ago, have played a major part in creating the chronic disability picture we see today; in the process of curing diseases which heretofore were killers, residual disabilities have been produced on a scale never before seen.

The very fact that we now are adding years to the lives of victims of chronic disease gives us a great challenge and an opportunity. The challenge is illustrated by the fact that, of the estimated two million disabled persons in this country who could profit from vocational rehabilitation services, some 88 per cent are disabled by chronic disease. Yet only a small fraction of these men and women receive such services, with the result described by Dr. Howard A. Rusk, an international authority on vocational rehabilitation: "Without proper services, victims of chronic disease go through a cycle that includes physical neglect, emotional trauma and vocational sterility."

This leads us to ask ourselves; "How can chronic disease programs reduce the social and economic burden of neglected disability?" One means is prevention, of course, and another is research into causes. But for a large portion of the disabled, rehabilitation is the only answer.

The significance of rehabilitation as a means of overcoming the disabling conditions wrought by chronic disease has been recognized formally by the Commission on Chronic Illness. In making its various recommendations public in

November, 1954, following the National Conference on Care of the Long-Term Patient, the Commission had this to say: "Rehabilitation is an innate element of adequate care and properly begins with diagnosis. It is applicable alike to persons who may become employable and to those whose only realistic hope may be a higher level of self-care. Not only must formal rehabilitation services be supplied as needed, but programs, institutions, and personnel must be aggressively rehabilitation-minded."

THE VOCATIONAL REHABILITATION PROGRAM

One major effort to compensate for the handicapping efforts of chronic disability is the public program of vocational rehabilitation. During recent years, this State-Federal program has been restoring to productive work and more satisfying lives from upward of 55,000 disabled men and women annually. Yet the gap between this number and the estimated 250,000 persons who come to need vocational rehabilitation annually serves to dramatize the extent of existing neglected disability. In 1954, 59 per cent of the disabled persons rehabilitated and restored to work through the public program had been victims of disease as distinguished from accidents and congenital conditions. This figure showed a continuation of the trend which had been evident for the past ten years; in 1945, the percentage was 42.8.

There is an interesting parallel between this and the age trend among those rehabilitated. In 1945, the median age at time of acceptance was 28. It has ascended steadily and reached 34 in 1954. By actual age groups, the same picture prevails. In 1944, for example, 4,493 disabled individuals age 50 or over were rehabilitated through the public program. By 1954, this figure had reached 9,936—an increase of more than 100 per cent.

The program operates in all states and in Alaska, Hawaii, Puerto Rico, and the District of Columbia. In 35 states, there are two vocational rehabilitation agencies, one for the blind and one for those with other disabling conditions. To finance the work, the Federal Government makes grants-in-aid to the states, which share in the cost and which carry out the program.

To be eligible for services, a disabled person must be of or near working age, have a disability which substantially interferes with satisfactory employment, and have a reasonable prospect of becoming suitably employed after rehabilitation services.

The disabled person receives a complete examination and evaluation—medical, vocational, and other—to determine eligibility and provide information, after which a rehabilitation plan is drawn up. He or she may receive part or all of a comprehensive range of services—medical, surgical, hospitalization, counseling, artificial appliances, training, and necessary equipment for a job, placement, and a number of supporting services. The program provides for all such persons, without cost, examination, counseling, training (in most states) and job placement and follow-up. Other services are provided without cost only to the extent the individual cannot pay for them.

The gap between the need for services and their availability exists because of three great blocks to our effort—lack of funds, lack of facilities, and lack of trained personnel.

NEW LEGISLATION

To help overcome the blocks, Congress, during its 1954 session, enacted three pieces of legislation which promise to have a profound long-term effect upon this country's efforts to make constructive headway against the problems of chronic disease: (1) *The 1954 Amendments to the Vocational Rehabilitation Act*, (2) *The Medical Facilities Survey and Construction Act*, and (3) *The 1954 Amendments to the Social Security Act*.

The 1954 Amendments to the Vocational Rehabilitation Act (Public Law 565) "broke the barrier," so to speak, in the three phases of funds, facilities, and personnel and, at the same time, introduced a new research program.

One of the significant developments of the last ten years has been the growing demand for rehabilitation centers in which the complex needs of the more severely disabled person may be evaluated and met by a team of experts. To help meet this demand, two complementary pieces of legislation were enacted into law. One was the incorporation into the Vocational Rehabilitation Act of provisions for grants to pay part of the cost of expanding present centers and converting buildings to this purpose, along with aid in equipping them and providing initial staffing. Similar aid is provided for the development of additional sheltered workshop facilities for the handicapped. Specific provisions were included in the 1954 Medical Facilities Survey and Construction Act for the construction of new centers on a comprehensive scale, and particularly those needed in conjunction with hospitals and medical teaching institutions.

In passing the latter Act (Public Law 482), the Congress capitalized on the successful experience of the Hospital Survey and Construction program, to cope with the mounting needs for physical facilities to serve the chronically ill and other disabled persons. Through this new Act, the Congress provided for Federal sharing in the cost of surveying community needs and constructing four specific types of facilities—chronic disease hospitals, rehabilitation facilities, nursing homes, and diagnostic or treatment facilities.

While research has been a beacon shining ahead in the development of medicine, it is unfortunate but true that there has been extremely little research to guide rehabilitation except in relation to certain clinical phases of medicine. As a result, there have been and are vast areas of the total rehabilitation process which have never been adequately explored and for which no comprehensive plans for investigation have ever been drawn up. A parallel need has existed for additional studies and demonstrations which, while not in the nature of research, would gather into organized and useful form the experiences of communities and agencies and pass them along to similar groups faced with similar problems.

The new Vocational Rehabilitation Act therefore included specific authority to carry out a program of grants for Special Projects to public and voluntary nonprofit groups in support of research, demonstrations, and studies, as a start in building new knowledge which we may one day put to use to transform today's failure into tomorrow's success.

The personnel shortage in rehabilitation has been mushrooming during the past five to eight years, when the demand for rehabilitation services has grown

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at a phenomenal rate, but without any accompanying organized plans to produce the trained staff needed to render services.

The Congress recognized the urgency of this need and incorporated into the Act provisions for a program of Federal grants in support of the expansion of rehabilitation courses and curricula in teaching institutions and for traineeships for selected students. Under this program, now entering its second year, 102 colleges and universities have established or expanded their curricula to teach courses to a variety of professional rehabilitation groups—physicians, therapists, rehabilitation counselors, social workers, psychologists, administrators. At present, 448 trainees are enrolled in approved schools for regular courses, with another 151 taking intensive short-term courses.

The 1954 Act introduced a new system of financing for the public program, providing for three types of grants: first, for *basic support* of state agency rehabilitation services, with the Federal share geared to population and per capita income of the individual state; second, for *extension and improvement* of services, on a project basis, with the Federal share based on state population; and third, *special project* grants, made on the basis of individual project applications from public or voluntary agencies, to carry out research demonstrations and studies or to provide facilities or services which will help solve national or regional problems in rehabilitation, with the Federal share not specified in the Act.

Under the new financial arrangements, the Congress has twice voted substantial increases in Federal funds in order that the expansion of rehabilitation in this country may proceed rapidly. Many states have responded by increasing the state funds devoted to this work.

Perhaps one of the most significant features of the new Act is the provision whereby local communities may establish and operate their own vocational rehabilitation agencies under the general supervision of the state agency. This permits cities and counties to establish a local rehabilitation program on a basis similar to local schools, public welfare, and other community agencies, with local funds matched by state and Federal funds. A community would, as a result, have a much greater ability to gear the amount and type of rehabilitation services to actual local need.

In broadening the Old-Age and Survivors' Insurance provisions of the Social Security Act, the Congress in 1954 took several important steps which will improve the nation's ability to deal more constructively with problems of chronic disease and disability. Previously, the worker in covered employment who became disabled and unable to work suffered a substantial reduction in his retirement income when he reached the age of 65 and began to draw payments. Under the new amendments, the worker who has been disabled for six months or longer, and who meets the minimum eligibility requirements, may apply to have his retirement rights "frozen" for the period of his disability. As a result, when he reaches the age of 65, he is assured of retirement benefits without having the amount reduced because of the period when he was disabled.

In enacting this feature, the Congress stressed the rehabilitation concept, so that the Act provides for (1) the prompt referral of all such applicants for "freeze" rights to the state vocational rehabilitation agency; and (2) a state agency to

determine whether the person is in fact under a disability which prevents him from engaging in substantially gainful employment, with the state vocational rehabilitation programs indicated as the agency of choice.

Both of these procedures—for making disability determinations and for referral of cases to the state rehabilitation agencies—are now in operation in all states, with the rehabilitation agencies making determinations in 47 of the states and territories (and state public welfare agencies in the remaining 5).

THE FUTURE

Almost daily, we are getting better tools to work with in serving the chronically disabled. They come from widely different directions—research findings, improved equipment, new laws, more and better trained professional personnel. Yet the very emergence of these gains has served to emphasize, as probably the most important job ahead, a basic question which has been at the heart of chronic disease work for years: how do we get better results with what we already have, and with all the advances which we know will become available in the next few years?

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Two things, it seems, are fundamental to answering the question. First, we will proceed only as fast as public understanding and support will permit us. This has been demonstrated many times. The experience gained in developing the splendid public health service we enjoy today can serve as a guidepost. Chronic disease, though a pervasive and technical challenge of enormous magnitude, can and must be portrayed to the American people by leaders in this work.

Second, we simply cannot expect to make really significant headway until we achieve a much greater confluence of interests and activities between public health, clinical medicine, rehabilitation, and certain other services which are integral parts of the picture of community life. Until this is done, we are certainly not able to present a clear composite picture of the problem, or of solutions, to civic and governmental leaders.

The Commission on Chronic Illness, in 1954, adopted several principles which are basic to a real understanding of the nature of chronic illness and what to do about it. These emphasize the urgent need to *look at the chronic illness picture in its entirety*, rather than attempting to deal with pieces of the problem individually, and to make comprehensive across-the-board community plans on this basis. Nowhere is there a better illustration of the fusion of health and socioeconomic problems than in the needs of the chronically ill. It is totally unrealistic to think of meeting those needs through unilateral efforts in facilities, clinical medicine, income maintenance, rehabilitation, or social casework. *But the sum of these services, focused upon an intelligent and well-defined community plan for the chronically ill*, can get constructive and lasting results—and at a smaller cost than hit-and-miss methods.

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RESULTS OF REHABILITATION IN THE FIELD OF WORKMEN'S COMPENSATION

INTRODUCTION

The National Safety Council compilation of statistics for the year 1953 (the latest year surveyed) indicates that there were 2,000,000 work accidents which caused a total production loss of 45,000,000 man-days and a total cost in loss of wages, medical expense, compensation benefits, and other administrative expenses of $1,650,000,000. If we add to this latter figure the so-called hidden, or indirect, cost of the lost production time, it raises the total estimated cost of work accidents in 1953 to the staggering total of $3,150,000,000.

THE BROADENING CONCEPT OF WORKMEN'S COMPENSATION

Our first compensation laws provided a comparatively simple schedule of weekly benefits for disability resulting from accidents arising out of and during the course of employment. More statutory changes have been made in workmen's compensation laws, however, than in any of our other social laws, and virtually all have been to increase or broaden the benefits. This is well illustrated in Massachusetts. When the Law was drawn in 1911, the maximum period for which compensation could be paid was 300 weeks and the maximum amount was $3,000. Payment of medical expenses was provided for only a two-week period following the injury. Today, benefits are payable for life for total permanent disability and medical benefits may be awarded as long as needed without limit. To these are added substantial schedule awards for loss of or permanent damage to body parts, for the loss of bodily functions, and for disfigurement.

Not all statutes are so generous. However, 23 of our existing compensation laws provide disability payments for life for total permanent disability and in 35 of the jurisdictions medical benefits may be awarded for as long as the injured worker lives, virtually without limit. In addition, during the past fifteen years the cost of medical treatment has nearly doubled and the cost of hospital services has tripled.

In addition, during the past ten years there has been a marked trend on the part of industrial boards and commissions to hand down decisions awarding compensation for disabilities that have resulted from accidents or so-called accidents that have aggravated degenerative diseases. This is a new experience in workmen's compensation, because when the diseases of old age which are degenerative in character are aggravated by industrial injury, these disabilities usually become permanent. Such diseases are usually progressive whether they have been modified by industrial injury or not.

It is, of course, a well-known concept in workmen's compensation that the employer accepts the employee in the condition which he finds him, and if the

employee meets with an accident which aggravates a pre-existing condition causing disability, the employer is responsible for that disability just as though the accident had been the sole cause. During this period, there have been some leading decisions handed down on heart cases in large industrial states, such as New York and Massachusetts. These decisions have awarded compensation to employees in cases of disability and to dependents when death ensued as the result of heart attacks which occurred while the employee was on the job.

In a number of these decisions no untoward incident took place which could be pointed out as a specific accident but rather the cause of disability or death was attributed to the arduous nature of the work, nervous tension or emotional strain caused by the work. Similar decisions have been handed down in cases of arrested tuberculosis, cancer, arthritis, asthma, diabetes mellitus, and other progressive types of degenerative disease. There has been a tendency to put the cost of disability and death due to degenerative diseases onto industry. As the result some industries have taken a defensive position not only with regard to the employment of persons who have been known to have heart ailments or other degenerative diseases but to persons in the older-age groups who, they felt, were subject to these conditions.

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In New York State developments in medicine have led to new theories of causal relationship of certain diseases to industrial employment which have resulted in awards that are proving to be very expensive. These are illustrated by findings that have been handed down, holding Dupuytren's contracture in the hands to be an industrial disability and aseptic or bone necrosis in the long bones of men who have worked under air pressure to be similarly compensable. Medical opinion indicates that bone necrosis in these patients is a deterioration of bone due to the clogging of terminal blood vessels caused by bubbles of nitrogen in the blood. Premiums of 50 per cent of payroll to insure such an operation have been quoted in New York.

In recent years a number of decisions have been handed down supporting awards for loss of hearing due to noise, even though the worker suffered no loss of time or reduction in wages. Industrialists view with alarm the rising cost of these responsibilities placed on industry.

The broadening concept of workmen's compensation has also had its effect on medicine. It is interesting to note that in comparatively recent years, 15 of the nation's 72 medical schools have established departments of legal medicine. In other schools required and elective courses are offered. In five medical schools comprehensive graduate courses are available.

EFFECTS ON INDUSTRY

Industry may well ask how it can find relief from this growing burden of the cost of workmen's compensation cases.

In New York State, industry has been endeavoring to take action through its leading trade associations. Associated Industries of New York State, Inc., for several years has been endeavoring to get relief through legislation but without success. The Commerce & Industry Association, Inc., has also asked the Work-

men's Compensation Board for hearings on its need for relief by legislation and through changes in the laws.

When one considers the long line of decisions handed down in the various states which causally relate to industrial employment so many of the diseases characteristic of old age, it is not surprising that industry is timid about hiring the elderly.

Similar timidity also exists with regard to the employment of younger people who are known to have physical handicaps. Unless methods can be found to place older workers and persons with physical abnormalities on safe and productive jobs, the problem of the dole is going to grow greatly in the present generation and the productive power of the country will be held back considerably from its maximal strength.

The solution to the problem of the employment of individuals who are suffering from progressive or degenerative diseases is not an easy one. Medicine is going to need to help us on the scope of employability of persons suffering with heart diseases, arrested tuberculosis, and many other medical conditions. These questions not only involve determination of when persons suffering with those conditions are safe for employment but how long it is safe to retain them in employment. In using the word "safe," I have in mind safe for the welfare of the individual himself as well as a safe risk for his employer. Because we are in the evolutionary development of this problem in workmen's compensation, the answer to these questions has not been found. Medical research is needed and undoubtedly will help to point the way as to how these people can be employed more safely than we now know.

Further study of second injury fund provisions may point the way as to how compensation loss may be spread and protection can be given to the employer when such persons are hired or retained in employment. Also with the aid of medicine we may get clearer determination of what constitutes industrial aggravation of these pre-existing conditions so that industry will not feel as some do now that they are being penalized by retaining in their employ persons who are suffering with conditions of degenerative disease.

It seems unthinkable that the alternative of these suggestions should be adopted; that is, that older-age persons and younger persons who may have some medical disorders are not employed because industry fears the consequences of hiring them. The loss of this great potential of production could change our whole economy with consequent loss to national income and tax revenue. Instead of tax producers, these people would be tax consumers. In this day of technologic progress in the production of the nation's goods, experience and know-how are of great importance. Need for the common laborer is diminishing and need for the skilled and scientific worker is increasing. Therefore, it would seem that we need the skills of these experienced people. All of these factors demand that we proceed with medical, legal, and scientific research to make practical the employment of the medically disabled as well as those with physical deformities.

The acuteness of these growing problems became apparent to Liberty Mutual with the advent of World War II, because of its responsibilities both to industry and to labor as a carrier in the workmen's compensation system. The

Company decided that much more scientific knowledge should be applied to the management of disability because change could not be expected in the trend of legislation, to broaden the benefits, nor in the trend of decisions, to broaden the interpretation of disabilities.

METHODS USED TO REDUCE LOSS IN INDUSTRIAL ACCIDENTS

A research was undertaken of the problems of disability. Examination of many cases of long-term disability disclosed that although the reason for such disability were multiple, they did form a pattern of causes. It was felt that some relief could be obtained through some of the new developments in medicine if properly applied. A substantial number of the cases had not made early progress toward recovery, owing to complications in the traumatized or fractured part, or to complications of the injury being superimposed on some previously existing bodily ailment.

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In studying these causes of disability, it often seemed evident that errors in diagnosis had been made, that intensive diagnostic study should have been made earlier in some adequate hospital or clinic facility, and that the diagnosis and treatment should apply to the man as a whole as well as to the injured part. The action taken was to enlist the aid of consulting specialists in some 53 of our larger industrial communities to act as medical advisers. Their function is to review the medical progress being made on all cases of serious disability. Because these are most often cases of fracture or other trauma, the Company has utilized the services of orthopedists with special experience in traumatic work. They are asked to review medical histories, to consult with treating physicians, and to recommend diagnostic work or technical procedures that may be in the best interest of the patient. This is in no way aimed at removing cases from the care of treating physicians but is directed at giving the physician any assistance that can be provided. These reviews may confirm the treatment or they may reveal the need for further x-ray, laboratory, or diagnostic studies. It is a process of determining what a problem case needs and then offering to provide it, whatever or wherever it may be.

The study of serious disability cases revealed a second large group that had progressed well through surgery and surgical healing, had been discharged from the hospital as cured, and yet months or even years later the individuals had not returned to any form of work. Again the causes were multiple, but still they formed a pattern of continued disability due to stiff joints, atrophied muscles, fear of recurrent injury, lack of confidence, or combinations of residual disability superimposed upon some previous ailment.

Study of existing facilities for physical restoration in the United States and Canada convinced the Company that a service combining diagnostic study with physical restoration could do much to assist treating physicians to rehabilitate many of this latter group of cases. To provide a place where such a service could be carried out, Liberty Mutual's first rehabilitation center was opened in Boston in June, 1943. Subsequently, a second center was opened in Chicago in January, 1951. These centers have consulting staffs of physicians qualified

in orthopedics and experienced in the field of trauma. They examine all patients on admittance in order that the exact condition of the injury may be known and rehabilitation therapy correctly prescribed. Also on the staffs are physicians qualified in internal medicine. Each patient has a chest x-ray, together with a complete physical examination, supported by any laboratory studies that may be indicated, in order that the staff may deal adequately with ailments which might complicate recovery. The full-time staffs of the Centers consist of physical therapy and occupational therapy technicians as well as prosthetists and trained counselors.

The equipment for treatment includes examining rooms, routine physical therapy and hydrotherapy devices for the application of heat, and many standard types of machines to provide physical therapy exercise. The Centers also contain well-equipped workshops and departments of recreational therapy where graduated exercise can be carried out under the supervision of occupational therapists, where work tolerances can be observed and developed until actual work ability has been attained. The prevocational undertakings are selected to fit the patient's interest, to encourage him to re-establish his confidence, and to harden him to actual work ability.

A comparatively recent study of 2,866 cases of all kinds treated at the Boston Rehabilitation Center reveals some statistical facts of interest. The average age of male patients has been 44.4 years and the average age of females 43.0. The average length of time from the injury or surgery to admission to the Center has been 6.9 months. The average length of treatment has been 41.5 days. Of the total of 2,866 cases, 2,442 (85 per cent) were improved by treatment. Of those improved by treatment, 2,010 (82.3 per cent) were returned to work. The average cost of the rehabilitation was $594.

The results being obtained at our Chicago Center are similar to those at the Boston Center. A statistical study of 730 cases reveals that 659 were definitely improved by treatment. Of those, 540 cases (81.9 per cent) were returned to work.

REHABILITATION OF AMPUTEE CASES

Because the Company's long experience in the handling of compensation cases revealed that comparatively few amputees had mastered the use of artificial limbs, we included in our Centers a service for amputees. This service is conducted under the guidance of physicians experienced in problems of the amputee, with the assistance of trained prosthetists who are technicians qualified to manufacture and fit artificial limbs. When problems of stump shrinking, flexion deformities, and muscle weakness have been adequately solved, guidance is given by the prosthetists in the selection of an artificial limb that will best suit the patient's circumstances and the kind of employment which is comtemplated for the amputee. Once the selection is made, careful measurements are taken and the limb is then manufactured to suit the size, weight, posture, etc., of the individual. The completed limbs are carefully fitted and the amputees are then taught to use their limbs correctly. This is carried out in such precise fashion that, even in the case of bilateral arm and leg amputees, they are taught to be entirely

self-sufficient. This includes the ability to put on their limbs, make their toilets, dress themselves, eat, travel on public transportation, drive cars, and use the tools of their future employment.

Virtually all employees who have used these services wear their devices sucessfully, and three-fourths of those who have completed training have returned to remunerative employment, including men who have lost both legs above the knees and men who have lost both arms above the elbow. Significant statistics on the amputee program at the Boston Center disclose that of 252 patients on whom treatment has been completed, 191 returned to work. Of this number of amputees, 18 were individuals who had lost more than one member, that is, they had lost both feet or legs or both hands or arms. Of these 18, 14 were able to return to work.

The success of the rehabilitation centers is usually measured in terms of the patients who have been returned to work, because that is objective proof to industry of the merit of these services. This might well lead one to the concept that all of those who had not been returned to industry were failures. Nothing could be further from the truth. In many of these serious cases where rehabilitation does not succeed in returning an employee to an occupation, it does succeed in improving him to the point that he does not need to live in a hospital, to have nursing care or even attendant care. In many cases, even of the most serious injury, these people have been taught to take care of all of their own personal needs, to be independent and to enjoy many physical activities. These are very real accomplishments. Every patient so rehabilitated releases a hospital bed, a trained nurse and attendants. These, of course, are financial gains because they relieve the tremendous costs of hospital, nursing, and attendant care. They are social gains because they are of great benefit to the individual as well as the community.

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REHABILITATION OF SPINAL CORD INJURY CASES

Dramatic proof of this fact is found in Liberty Mutual's experience in the handling of paraplegia and quadriplegia cases, which are the most serious types of injury that occur in industry. These are cases where the employee suffers a fracture or dislocation of the spinal column which in turn has severed or severely damaged the spinal cord. They may require a lifetime of hospital, special nursing, or attendant care unless heroic methods of rehabilitation can be applied. The Veterans Bureau has perfected methods which teach paraplegics self-care, how to walk with crutches, how to drive cars with special hand controls, and how to perform sedentary work.

At the present time Liberty Mutual has 111 open paraplegic cases and practically all of them have an indefinite period of life expectancy. Some may live out a virtually normal span of life. Comparatively few civilian services of rehabilitation for paraplegics have been developed. Through the cooperation of Dr. Donald Munro, the Liberty Mutual Insurance Company has developed such a program. The service, which was formerly provided by Dr. Munro at the Boston City Hospital, is now established under his supervision at the In-

dustrial Rehabilitation Department and Neurosurgical Services wnich was opened in October of this year under the joint sponsorship of the Massachusetts Memorial Hospitals and their affiliated Medical School, Boston University, and Liberty Mutual Insurance Company.

Of the 111 open paraplegia cases, the Liberty Mutual is carrying reserves of $6,719,000 to pay for future indemnity and medical benefits which will be due. Rehabilitation has actively been undertaken on 85 of these paraplegia cases and has been completed on 66 of them. Of that number 32 (48 per cent) have returned to work or are in business for themselves. Of the remaining 34 patients, 23 (35 per cent) are living at home but without the need of nursing or attendant care; 9 (14 per cent) have been discharged from hospital but still require some degree of paid attendant care; and 2 (3 per cent) still require hospital care. (Table I.)

TABLE I. STATISTICS ON THE 66 CASES REHABILITATED

Total estimated indemnity and medical cost of completed cases if not rehabilitated...	$6,812,509
Total estimated indemnity and medical cost of completed cases as of this date....	$3,683,025
Total estimated saving in indemnity cost on completed cases by rehabilitation....	$72,120
Total estimated saving in medical cost on completed cases by rehabilitation.....	$3,057,364
Gross estimated saving in indemnity and medical cost of completed cases.....	$3,129,484
Cost of rehabilitation of completed cases.....	$676,771
Net estimated saving in indemnity and medical cost of completed cases.....	$2,452,713

It will be noted from these figures that the amount that has been saved on compensation indemnity payments is very small. This is because most compensation laws state that if a man has lost both legs by amputation or the use of both legs as the result of an injury, he will be deemed to be totally and permanently disabled and will receive maximal payment under the law. For these reasons little money for indemnity can be saved through a rehabilitation program. The savings that have been made on future hospital, nursing, and attendant care, however, are tremendous.

REHABILITATION NURSE PROGRAM

The rehabilitation of seriously injured workmen is not accomplished through the application of any one superior type of medical service but rather through a coordinated program of contributing technical services. Rehabilitation is, therefore, dependent upon accurate diagnosis, competent surgery, a program of physical restoration, vocational re-education in some cases, and appropriate placement on a safe and productive job in all cases.

Management and coordination of the above phases of a program for an injured man are required in every case. To handle this responsibility, Liberty Mutual has employed and trained degree nurses, who are called Rehabilitation Nurses. They do the necessary counseling of the injured man to get his cooperation with the needed medical or surgical services. They plan and arrange

the programs for physical and vocational rehabilitation. Plans for placement may be made long before rehabilitation has been completed. These nurses work out the details of placement with the former employer or with a new employer so that the work the rehabilitated person is to undertake fits his ability and his aptitude. Above all else, the job must be safe for the worker, who may be permanently handicapped, and it must also be productive or the placement will not stick. Much skill is required in carrying out successful placement. It calls for knowledge of work requirements in industry and understanding of the physical abilities of handicapped or aging workers.

Within this knowledge of placement lies the key to the over-all problem of harnessing the productive capacity of our thousands of handicapped or partially disabled people.

CONCLUSION

Industry, labor, and society are best served when the legal and medica aspects of industrial disability are so harmonized that injured workers are returned to safe and productive jobs at the earliest possible date.

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THE TREATMENT OF TRIGEMINAL NEURALGIA

Facial neuralgia as a clinical entity dates from John Fothergill's classical description in 1773, though it was not until the work of Magendie and Bell in the early nineteenth century that facial pain could be related to the functions of the trigeminal nerve. The French term "tic douloureux" has had prolonged usage in the medical literature as well as among lay persons, though other terms such as "major trigeminal neuralgia," "paroxysmal trigeminal neuralgia," and "trigeminal tic" are commonly employed.

It is of interest to quote from Fothergill's description,[1] which leaves little to be added: "This affection seems to be peculiar to persons advancing in years, and to women more than to men. I never met with it in anyone much under forty . . . . The pain comes suddenly, and is excruciating; it lasts but a short time, perhaps a quarter or half a minute, and then goes off; it returns at irregular intervals, sometimes in half an hour, sometimes there are two or three repetitions in a few minutes . . . . The kind of pain is described differently by different persons, as may be reasonably expected; but one sees enough to excite one's compassion, if present during the paroxysm . . . . It returns full as often in the day as in the night. Eating will bring it on in some persons. Talking, or the least motion of the muscles of the face, affects others; the gentlest touch of a hand or a handkerchief will sometimes bring on the pain, whilst a strong pressure on the part has no effect."

It is wise to think always of "neuralgia" as pain in a sensory nerve distribution secondary to some pathologic lesion affecting the nerve. Trigeminal pain or neuralgia is often secondary to causes such as dental caries, osteomyelitis, sinusitis, or neoplasms invading the base of the skull. Occasionally primary neoplasms of the trigeminal ganglion, neoplasms within the posterior fossa, or cerebral aneurysm, will cause paroxysmal facial pain. Trigeminal pain may also occur in patients with multiple sclerosis. It is only when such causes of the pain have been eliminated that we may speak of paroxysmal trigeminal neuralgia as a clinical entity.

The causes of "primary" trigeminal neuralgia are obscure, for no consistent lesion has been found post mortem. It has often been suggested that the original cause is dental infection with extension along the sheaths of the dental nerves. Vasomotor changes in the trigeminal ganglion or local arteriosclerotic changes have been suggested by other authors. There is no agreement as to whether the lesion provoking the pain lies in peripheral branches, in the ganglion, or in the central trigeminal connections. One fact only seems definite, that the pain can be abolished by destroying the trigeminal branches to the affected region of the face, and this has been the basis of most varieties of surgical treatment.

Trigeminal neuralgia is chiefly a disease of older people, and cases are rare under the age of 50. With our aging population we may expect to encounter it more and more frequently, and the need for satisfactory treatment becomes a matter of increasing urgency.

A glance through the *Index Medicus* covering the medical literature of the nineteenth century reveals literally scores of apparently successful remedies for facial neuralgia; but it is obvious from our present-day vantage point that there was no satisfactory medical treatment. Avulsion of peripheral branches of the fifth nerve with relief of pain was practiced occasionally during this period, for the most severe cases.

In recent times many attempts have been made to find an effective medical treatment for a condition which seems to have no underlying "lesion." Encouraging results were reported a few years ago from the use of large parenteral injections of thiamine chloride and B complex, and these are still widely used. More recently, there have been enthusiastic reports on the use of massive doses of B_{12},[2,3] though in severer cases this form of treatment is often disappointing.

The newest medical development in the treatment of trigeminal neuralgia is the use of stilbamidine, by mouth or by intravenous injection. This drug produces within a few weeks an impairment of trigeminal sensation associated with paresthesias of the face, and a gradual disappearance of the paroxysms of pain.[4,5] Apparently a form of chemical neuropathy is produced by the stilbamidine. It is too early to evaluate this form of treatment. One obvious drawback is the delay between the beginning of treatment and the onset of relief. Another drawback seems to be the occurrence of facial paresthesias, which may become very intense and bothersome. While Woodhall[6] feels that stilbamidine is a valuable adjunct, it is wise to confine the trial of this toxic drug to special clinics, until more is known about the long-term results of its use.

Modern surgical treatment of trigeminal neuralgia began when Frazier and Spiller (1902) developed a safe technique for intracranial section of the posterior root of the trigeminal nerve. This has become a standard neurosurgical procedure, which has not been displaced by Sjöqvist's newer operation of trigeminal tractotomy (1938).

About the same time, new techniques were developed for alcohol injection of the main trigeminal branches, or even of the ganglion itself,[7] which in skilled hands have given results as satisfactory as those of surgical operation. These procedures are particularly valuable in aged patients and in others where the operative risk is great. Recently, Jaeger[8] has reported satisfactory results from the injection of small quantities of boiling distilled water, rather than alcohol, into the trigeminal ganglion.

The most recent neurosurgical development has been the operation of "decompression of the trigeminal root and posterior part of the ganglion" introduced by a Danish neurosurgeon, P. Taarnhøj.[9,10] Proceeding on the theory that the neuralgia may be due to pressure on the trigeminal structures by the overlying dura, he dissects the dura from the underlying ganglion and posterior root, without interrupting any sensory fibers, thereby avoiding many of the drawbacks of the standard posterior root section. The surprising thing is that at least 50 per cent of patients who have undergone this or some similar procedure have remained free of pain, when studied at least a year later. This procedure has been taken up enthusiastically by neurosurgeons in this country and abroad, and several modifications of the technique are being tested. It will require a

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period of years to evaluate these new procedures, but the prospect of pain relief without the customary trigeminal sensory loss is most encouraging.

Until experience with these newer medical and surgical methods has broadened, it is wise to be somewhat conservative in outlining treatment. First, it is important to make certain in every case that all demonstrable organic causes of trigeminal pain, intra- or extracranial, have been eliminated. Treatment with massive doses of B_{12} is quite harmless, and worthy of full trial. Trichlorethylene inhalations usually give only transient relief. Where the pain is localized to the second or third trigeminal division, an alcohol injection close to the corresponding foramen of exit will give complete relief of pain for a year or more. This should be the next step, if medical treatment has failed. There is also a place for avulsion of the supraorbital or infraorbital nerve (instead of alcohol injection) in some cases, though this, too, will rarely give relief for more than a couple of years. Injection of the ganglion itself has an extremely limited place, unless carried out by a very experienced operator.

In view of the success of the newer intracranial techniques, some neurosurgeons may wish to employ this procedure in every case. However, there is still a place for posterior root section, particularly in the older patient with a severe form of neuralgia, and where sure relief from pain is essential. Posterior root section, partial or complete, is also indicated, where previous alcohol injection has given relief for a year or more, in order to obtain a permanent result. Some surgeons prefer partial root section by the posterior fossa approach of Dandy (1925).

We still remain completely ignorant of the fundamental causes of trigeminal neuralgia. It is fair to say, also, that its treatment is still unsatisfactory. Nevertheless, in the past five years, new and promising methods of treatment have been introduced which are still undergoing appraisal. Eventually, they may lead to real improvement in our methods of treatment and a better outlook for the patient.

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Book Reviews

ADVANCES IN INTERNAL MEDICINE. Volume VII. Edited by W. Dock and I. Snapper. Pp. 311; indexed. Chicago, 1955, Year Book Publishers. Price $11.00.

There virtually is no end to the mounting flood of information of varying validity which threatens to engulf the generalist who continues to hope that he can keep abreast of new concepts. In response to the desperate state of the general reader the literature now bulges with a swelling supply of summarizing, simplifying, and sometimes stultifying reviews. Some of these reviews are pedestrian and hackneyed, yielding little more than a list of citations to the literature collected from similar reviews published the year before. Other reviews provide scholarly syntheses of the growth of knowledge in a specific area, together with fresh critical interpretations, and on rare occasions indulge in sprightly speculation. This reader must confess to the gloomy impression that, by and large, recent years have seen the emergence of a modified Gresham's Law applying to this special field: bad reviews drive out good.

It is on this account that it becomes a pleasant task to report that the tradition of excellence established by the earlier volumes of these *Advances* is continued, for the most part, in the present issue. The varied fare is indicated by the following list of the essays and essayists who have contributed.

Pathogenesis and Treatment of Renal Lithiasis—Newer Concepts." A. J. Butt.

"Hepatic Coma." C. S. Davidson.

"The Pathophysiology of the Pancreas." D. A. Dreiling and H. D. Janowitz.

"Clinical Significance of Serum Mucoproteins." E. M. Greenspan.

"Advances in Physiology of Clinical Disorders of the Adrenal Cortex." J. W. Jailer.

"Diseases of the Pericardium." V. A. McKusick and A. M. Harvey.

"The Nephrotic Syndrome." J. B. Squire.

"Applied Pulmonary Physiology." D. J. Stone.

Joseph L. Lilienthal, Jr.

LEGAL MEDICINE, PATHOLOGY AND TOXICOLOGY. By Thomas A. Gonzales, M.D., Morgan Vance, M.D., Milton Helpern, M.D., and Charles J. Umberger, with introduction by Harrison S. Martland, M.D. Ed. 2. Pp. 1370, with 658 figures, indexed. New York, 1955, Appleton-Century-Crofts, Inc. Price $22.00.

This book represents a complete revision and enlargement of the first edition published more than a decade ago. It is divided into forty-seven chapters and an appendix. There is included an historical summary of medicolegal investigation in America with the evolution of Medical Examiner systems. Excellent chapters are directed to the problems of identification, postmortem artifacts, the causes of sudden natural death, as well as the medical complications of injury. A brief section on war gases brings this subject up-to-date. The material on electrical burns is largely new and is the most complete available in any text. The important subject of blood grouping has been revised by Alexander Weiner and serves as an excellent reference material as well as a technical source on the use of blood grouping in paternity and criminal investigations. New subject matter, such as autopsy findings is embalmed bodies, the pathology of contusion of the heart, cerebal edema developing after trauma, and the development of alcohol postmortally due to putrefaction all illustrate the broadness of the scope of this text. One other interesting

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point is that the authors, in contrast to most other writers on the subject, state that the onset of rigor mortis is accelerated by cold as well as heat.

The illustrations are, for the most part, excellent. One improvement which one might hope will be made in subsequent printings would be to place the illustrations closer to the text describing the disease under consideration.

The book is by far the best medicolegal text available in this country or abroad. With the new chapters on "The Rights and Obligations of Physicians," "Malpractice Suits," and "Medicolegal Aspects of Psychiatry" as well as the excellent toxicology section written by Dr. Umberger, it is a "must" not only for the medicolegal pathologist but also for police investigators, prosecuting attorneys, and all interested in medicolegal problems.

Russell S. Fisher

THE CLINICAL CARE OF THE DIABETIC. By James J. Short, M.D., F.A.C.P. Pp. 84. Los Angeles, 1955, San Lucas Press. Price $3.95.

A long experience in the clinical management of diabetic patients is reflected in this brief manual. Since his interest in diabetes and its treatment began during the "Allen Era" of 1914-1921, the author has witnessed experiments with many types of dietary treatment and has had the privilege of experience in the pre-insulin era as well as in the period of insulin usage. It is reassuring to have a manual which states the objectives of treatment clearly and in physiologic terms. He would return blood sugar levels to normal and eliminate glycosuria as far as possible. He would restore normal weight by reducing the obese by a low-calorie diet. At the same time the maintenance of physical fitness and working efficiency are given an important place, with the avoidance of hypoglycemia through the adjustment of diet and insulin dosage, and, finally, consideration for patients' desires and avoidance of unnecessarily burdensome and restricted diets. Criteria for diabetic control include freedom from glycosuria before breakfast and frequently at other times during the day, the avoidance of hyperglycemia, and the complete control of ketonuria.

Various types of diet, including the old low-carbohydrate high-fat diet and the extremes of unlimited diets are discussed. He chooses to be a "middle-of-the roader." Excellent dietary tables are given.

The discussion of the nature of diabetes leaves something to be desired. Here brevity has lead to the sacrifice of the newer concepts of diabetes. He defines diabetes as a syndrome or disease resulting from a lack of insulin either relative or absolute. As a result of this the body is unable to utilize carbohydrate normally. He mentions the several experimental methods for producing diabetes. However, although all students agree that hypoinsulinism is the most important single central feature of true diabetes mellitus, few students today would consider that a sufficiently comprehensive definition. The diabetic state produced by pancreatectomy or by the injection of Alloxan or the injection of ACTH produces hyperglycemia and glycosuria but does not confer upon the animal or man thus treated the hereditary features of diabetes. Today with increasing knowledge of the many aspects of diabetes, the hereditary nature of true diabetes mellitus is more and more emphasized. The children of diabetic mothers show an extraordinarily high incidence of the diabetic state. Various combinations of genes may be involved in diabetes beginning at different periods in life. Some of these hereditary tendencies may be responsible in some measure for the premature development of vascular disease, neuropathies, and other features of clinical diabetes. These and other facts seem to make necessary a much more comprehensive concept of the growing diabetes problem of today.

Howard F. Root

AN HISTORICAL CHRONOLOGY OF TUBERCULOSIS. By Richard M. Burke, M.D., F.A.C.P., Ed. 2. Pp. 125, with 6 figures; indexed. Springfield, Illinois, 1955, Charles C Thomas. Price $3.75.

The second edition of this unique exercise in medical history is much improved. Moreover, it is a pleasure in this day of expanding (and expensive) texts by multiple authors to read a book written by one man who has wisely eliminated nonessentials to make room for the advances of the seventeen years' interval. The text has been largely rewritten and contains not an unneces-

sary word. The names and dates have been corrected wherever errors have been discovered. Illustrations and a bibliography have been added. The graphic outline folded in the cover of the first edition has been eliminated. With all these changes this little book remains, like the first edition, a pleasure to read or just to skim through, offering on every page unexpected nuggets of history. It is also a ready mine of information as a reference work for anyone preparing to speak or to write on the subject of tuberculosis. As such it should be in every medical library.

Julius L. Wilson

Erratum

Figs. 2 and 4 of the article by ALVIN F. COBURN, RICHARD C. BATES, J. WILFRID HAHN, and PRISCILLA MURPHY, entitled "Further Observations on the Diphenylamine (DPA) Reaction as an Index of Inflammation," which appeared in the February, 1956, issue of the JOURNAL, pages 140-153, are reprinted below in corrected form. Dotted lines have replaced solid lines in several places.

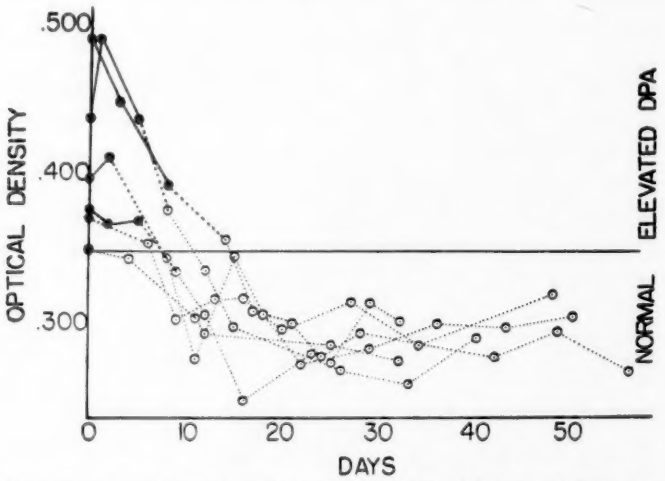

Fig. 2.—Simultaneous and prompt subsidence of both the CRP test and DPA determinations in six adults. Patients in whom both the CRP and DPA values returned rapidly to normal. Filled circles and solid lines indicate positive CRP tests. Empty circles and dotted lines indicate negative CRP tests.

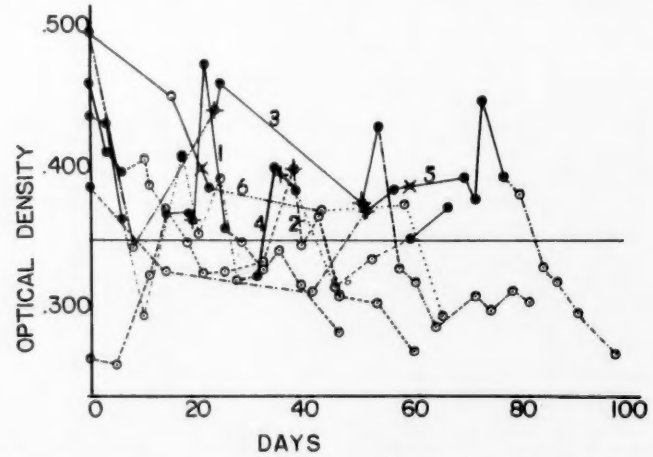

Fig. 4.—Serial determinations illustrating vicissitudes of the CRP and DPA determinations in six patients with rheumatic exacerbations. In each instance the DPA was elevated prior to or coincidental with the exacerbation. Filled circles indicate positive CRP tests. Empty circles indicate negative CRP tests. Crosses point to onset of exacerbation.

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